THIS ISSUE IS DEDICATED TO DR. J. BURNS AMBERSON

VOLUME 74 *December, 1956* NUMBER 6

THE AMERICAN REVIEW OF TUBERCULOSIS AND PULMONARY DISEASES

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MEDICAL SECTION OF NATIONAL TUBERCULOSIS ASSOCIATION

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THE AMERICAN REVIEW OF TUBERCULOSIS AND PULMONARY DISEASES

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Membership: All physicians and surgeons in the United States, Canada, and other countries who are interested in pulmonary and other thoracic diseases may apply for membership in the American Trudeau Society. The dues for active membership in the Society are $15 per year, which includes membership in the National Tuberculosis Association, copies of the Society's NEWS LETTER, and a subscription to the REVIEW and to the monthly BULLETIN of the National Tuberculosis Association.

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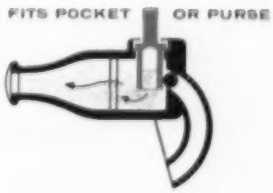

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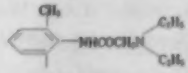

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2. McHenry, E. W.: Nutrition and Endocrine Function, Borden's Review of Nutrition Research, *16*:17 (Mar.-Apr.) 1955.
3. Ershoff, B. H.: Conditioning Factors in Nutritional Disease, Physiol. Rev. *28*:107 (Jan.) 1948.
4. Keys, A.; Brozek, J.; Henschel, A.; Mickelsen, O., and Taylor, H. L.: The Biology of Human Starvation, Minneapolis, University of Minnesota Press, 1950.
5. Samuels, L. T.: Progress in Clinical Endocrinology, New York, Grune and Stratton, 1950, p. 509.

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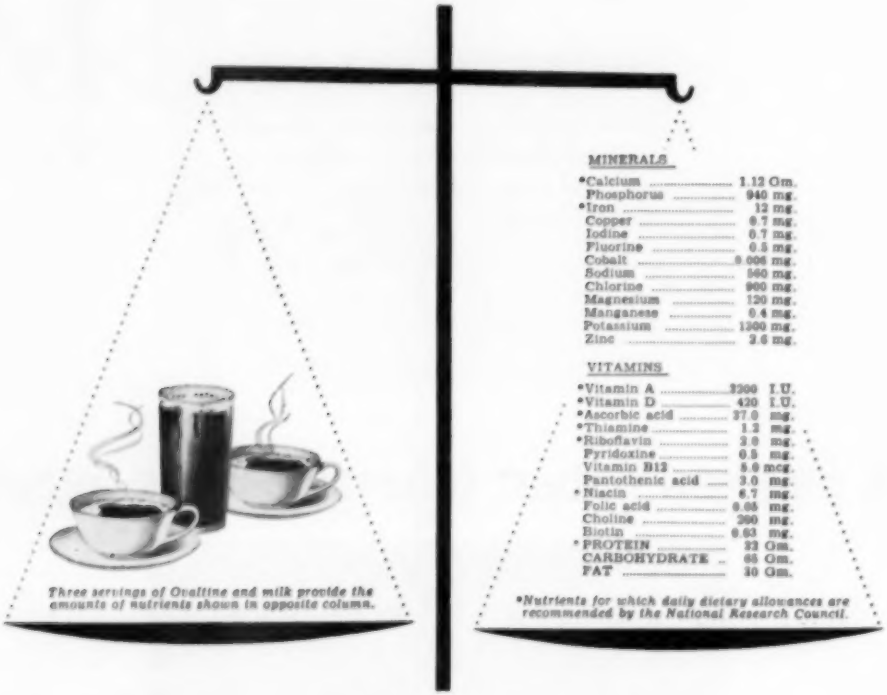

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Cohen, R. V.; Molthan, L., and Zarafonetis, C. J. D.: Clinical Studies of Various Forms of PAS (with special reference to plasma concentrations), *Diseases of the Chest* 30:418-428 (Oct.) 1956.

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*Miller, J.B., et al.: Ann. Allergy, 12:611, Sept.-Oct., 1954.

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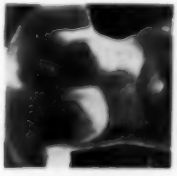

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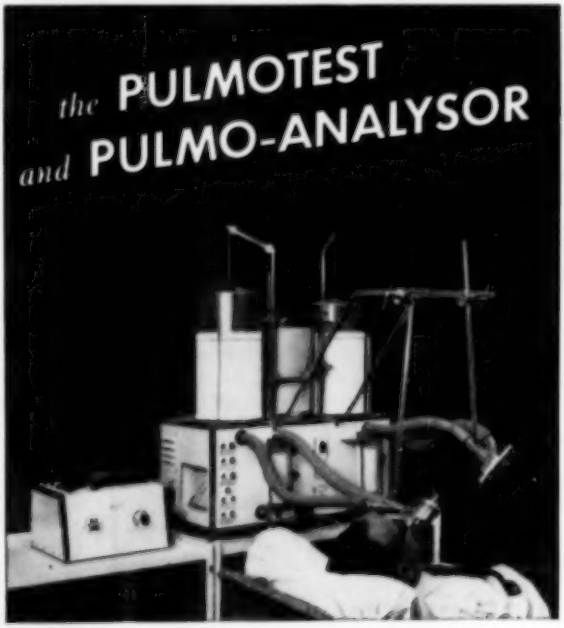

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[1]Dr. Samuel Phillips: *Calcium Benzoyl PAS*, Paper presented at 15th VA-Army-Navy Conference on Chemotherapy of Tuberculosis, St. Louis, Missouri, February 6-9, 1956.

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J. Burns Amberson

DEDICATION

This number of the REVIEW is dedicated to DR. J. BURNS AMBERSON. There are many reasons why this is most fitting and proper. Some of these reasons are presented in the Amberson Lecture and the recital of the accompanying ceremonies (pp. 821 and 980). But, taken together, they all mean the same thing: Dr. Amberson represents to a truly extraordinary degree the embodiment of the physician's ideal of the perceptive and compassionate man who can function with great effectiveness as an integrated scientist.

Long before the term "interdisciplinary" became a fashionable cliché, Dr. Amberson fairly radiated a judicious blend of many disciplines. With this "radiation" he has always shown a remarkable capacity to apply, and to communicate, the product of his wise blending of disciplines to his patients and to his students. In his consulting practice, which consisted almost entirely of young physicians and nurses, what he had to report, more often than not, represented a shattering blow to youthful strivings. Yet he has always been able to do this without crushing the youthful spirit. In a very real sense, the readers and the Editors of the REVIEW are all "old students of Dr. Amberson" and it is with the greatest of pride in our student role that we dedicate this number of the REVIEW to him.

November 10, 1956

THE EDITORS

THE AMERICAN REVIEW OF TUBERCULOSIS AND PULMONARY DISEASES

VOLUME 74 *December, 1956* NUMBER 6

THE J. BURNS AMBERSON LECTURE[1]

The Chest Service at Bellevue Hospital: A Better Mouse Trap

JAMES J. WARING[2]

I should like to pay noble tribute to this gentle man, this loyal friend, this wise counsellor, and great teacher. To do this without emotion I find difficult since my heart is over there with him. To avoid the hazards of sentimentality, abhorrent to him and also to me, I shall take refuge from time to time in jest, whimsy, call it what you will! If this were not so, you might well ask with Will Shakespeare: "Has this fellow no feeling of his business?" Wherefore, if I jest a bit, perhaps embroider some events, even draw upon my fancy for others, indulge me thus far. To avoid outward display of emotion one may say or do strange things. I have in mind the story of the bereaved widow of a miner killed in an accident. A committee of miners went to call on her. When she appeared in the door of her little cabin with face contorted with grief, they offered her a bunch of flowers and lamely tried to say a few comforting words. After swallowing her Adam's apple a few times, she burst out with "Go to Hell! Me heart is broke."

But what is all this about the Chest Service at Bellevue being a mouse-trap?

> If a man can write a better book, preach a better sermon, or make a better mouse trap than his neighbor, though he builds his home in the woods, the world will make a beaten path to his door.

According to my best researches, this should not be credited to Elbert Hubbard (1859–1915) but rather to Ralph Waldo Emerson (1803–1883). Its implication is clear. Over the years, the word has spread, over here, over there, among young and older graduates in medicine, that, if you wanted to learn chest diseases, you must find your way to Bellevue Hospital and sit at the feet of Amberson. I have never failed, myself, to time my visits to New York so that I could attend his clinic, and "ancient mariner" that I am, I consider myself one of his boys.

[1] Founded and sponsored by physicians of the Bellevue Hospital Chest Service, New York, New York. The Amberson Lecture will be delivered each year at the annual meeting of the National Tuberculosis Association and its medical section, the American Trudeau Society. An account of the ceremonies at the time of the first Amberson Lecture is presented in the American Trudeau Society section of this number of the REVIEW, pages 980 to 983.

[2] Professor of Medicine, Emeritus, University of Colorado Medical School; President, Colorado Foundation for Research in Tuberculosis, Denver, Colorado.

You are all aware that upon his retirement his former interns and residents tendered him a dinner and set up this lecture named in his honor.

I do not propose to review here all of his accomplishments, all of his contributions to our knowledge of chest diseases, nor all of the honors which have been bestowed upon him. Some of this I must do but then I shall turn to a more general discussion of the significance in our time of a great teacher in a special field.

Dr. Amberson was born in Waynesboro, Pennsylvania, got his bachelor's degree from Lafayette College in 1913, his doctor of medicine from Johns Hopkins University in 1917. He has received honorary degrees of doctor of science from his alma mater Lafayette (1944) and also from the University of Pennsylvania (1953). In 1948 he received a citation and medal from the Chinese Ministry of Health, Nanking, China. I note that, in addition to his honorary membership in the British Thoracic Society, he is also an honorary member of the Horseshoe Club of London. The full significance of this latter distinction was a bit obscure to me. From the name I fancied it was an organization of elderly men addicted to tossing horseshoes at metal pegs on Sunday mornings in Hyde Park, or perhaps a Club of owners of race horses, or a Club of jockeys or humble blacksmiths. Some inquiry has enlightened me. It seems to be an organization of generous Britishers dedicated to "squenching" the thirst of visiting Americans. Need I say more?

While on this subject of horses, on one occasion I found the patients in a certain British sanatorium in ecstasy, believe it or not! It seems that, playing a hunch, they had all most appropriately put their money on a horse named "Never Say Die" to win the Derby. Now I like to think that "Never Say Die" was fully aware of the burden of responsibility he carried in this race, not so much to protect the small wagers of a handful of tuberculous patients, but to protect their morale. If he lost, what a gloomy portent; if he won, what a happy promise for future recovery! Did he win? "Never Say Die" always wins!

But to continue the record, Amberson has been an honorary or corresponding member of numerous foreign tuberculosis associations from South America to India. During World War II, he was Chairman of the Sub-Committee on Tuberculosis, Division of Medical Sciences, National Research Council. Among his many editorial responsibilities, I refer you especially to his excellent chapter on tuberculosis in the Cecil-Loeb *Textbook of Medicine* and to his membership on the editorial staff of the American Review of Tuberculosis and Pulmonary Diseases.

As you know, from 1938–1955 he was visiting physician in charge of the Chest Service at Bellevue Hospital. Among his other affiliations have been: President of the Board of Trustees of the Trudeau Sanatorium, President of the Trudeau-Saranac Institute and Saranac Laboratory, and a member of the Advisory Board of the Colorado Foundation for Research in Tuberculosis. He received the Trudeau Medal of the National Tuberculosis Association in 1952 and is now Director of the New York Tuberculosis and Health Association, of which he was President from 1941–1946, and Professor of Medicine, Emeritus, College of

Physicians and Surgeons, Columbia University. His contributions to various medical journals number more than seventy-five.

So much for only part of the record! How any man who has had a little touch of what—shall I say—*used to be* a prevailing malady could permit himself to do so much, and how he could do it all so well and so apparently effortlessly, is beyond my comprehension. Does Providence provide the right man at the right time, dedicated to a great cause by laying upon him the accolade of *ein bischen tuberkulose?* I believe it so with Laennec, with Trudeau, and with Amberson. Hear what Sir Thomas Browne (1605–1682) has to say about this.

> Many haue thought it no Lost time to exercise their witts in the Praises of disease, some haue wittyly Commended baldness, others extolled quartane agues and some haue left incomiums of the Gout and think they extenuat the anguish of it when they tell what famous men, what Emperours and Learned Persons haue been severe examples of that disease and that it is not a disease of fooles, but of men of Parts and sences; but none haue attempted the incomium of Consumptions, which haue so well deserved as to this and the other world, giueing a Mercifull Conclution to the one, a solem preparation to the other: he that Prays against tormenting diseases or sudden death hath his Littany heard in this disease, which is one of the Mercyfullest executioners of Death, whose blows are scars to be felt, which no man would be killed to be free of, wherein a man is Led, not torn, unto his transition, may number his dayes and even Last hours and speak unto his Saviour when he is within a moment of him.[3]

Now, be not deceived. This man with quiet manner and gentle voice can be tough when occasion requires. I mind the time coming down from a medical meeting at Estes Park, just above Denver, when I got a flat tire. While I was leisurely taking off my coat and rolling up my sleeves, he captured the keys, opened the trunk, got out the tools, and began to jack-up the wheel. When I tried to take over—after all he was my guest and it was my car—he brushed me aside with a snappy "Get to Hell out of here!" Now, this was so out of character, at least as I knew him, that I fainted dead away. When I came to some minutes later and cautiously opened my eyes, I was not only amazed at the skill with which he was changing the tire (evidently he had had much experience with this) but painfully surprised at his lack of concern over my collapse. As a matter of fact, he did glance around at me once, whereat I quickly closed my eyes, and, I could be wrong, but I fancied I heard him murmur, "Serves you damn well right."

Well, in workman-like manner he finished the job, brushed the dust off his hands and clothes, picked up *my* hat and headed for a near-by creek. When he started back toward me with my hat full of water, I realized that my moment for recovery had come. Do you know, he chased me five times around the automobile before he would agree that I had revived! Truly, a tough hombre! This goes to show what Bellevue Hospital and commuting daily into New York will do to toughen a man's fiber! There was nothing subtle about this experience, but he is withal "a man of infinite resource and sagacity."

[3] "A Fragment from Sir Thomas Browne" by Henry R. Viets (New England J. Med., 1953, *249*, 455).

Consider this! When I received the invitation to visit the Brompton Chest Hospitals, I wrote our friend for advice as to professional and social responsibilities. One bit of advice he gave me was choice, he wrote "Act natural, but not too natural." Never have I received better advice! Even, at this very moment I am struggling more or less unsuccessfully to heed it.

Some days back, I wrote him about a successful fishing trip to Florida. Back comes a nice letter with introductory sentence: "First, let me congratulate you on your luck in fishing, and also on whatever skill may have entered into it." Can you beat that?

Now, in preparation for this occasion, I wrote many persons for certain information about our friend. I even wrote his secretary for some off-the-record incidents. That loyal and devoted and capable young lady evaded the issue by passing my inquiry on to Julia Jones and McClement! No man is a hero to his valet, but every doctor is or should be a hero to his secretary! (Denver papers please copy.) I wanted some of the amusing and human touches that inevitably happen in every doctor's life. For example, I recall Dr. E. L. Trudeau telling me about the young lady who, from inexperience, when told to take her things off, the doctor wanted to listen to her chest, appeared tearfully from behind the screen in his office without a stitch on!

Well, it occurred to me also to write Dr. S. R. Cutolo, Deputy Medical Superintendent of Bellevue Hospital, whose articles on Bellevue are now running in the Saturday Evening Post. I quote freely from Dr. Cutolo's reply:

> I regret that I am unable to mention any specific incidents or episodes of an amusing character. Dr. Amberson's personality is that of extreme seriousness and he imparts that seriousness to all who are privileged to listen to him. He is one of the most outstanding physicians that ever graced the wards of Bellevue Hospital. His demeanor is one of reticence, his knowledge of medicine is profound, his personality is one of detachment and geniality, his teaching capabilities are unparalleled, his conduct at conferences is one of humility and understanding, and at the conclusion of any of the conferences or ward rounds with Dr. Amberson one invariably feels a sense of delight and of achievement. I think that he has been a terrific inspirational force in the teaching of diseases of the chest, and I doubt that there is any other man, at least to my knowledge, who has given so much of himself in the dissemination of knowledge in pulmonary diseases.

The devotion of his former students, including in that term not only undergraduates but graduates, is a shining tribute to the man and the teacher. I could not use the title "teacher and student" for this address since the most inspiring teacher of our generation used it in 1892 in a talk at the University of Minnesota. At a leisure moment, I picked up my volume of *Aequanimitas* (collected addresses of Osler) and read again Osler's qualifications of a good teacher: enthusiasm, full knowledge of his special field, a deep sense of obligation; and then his summary of the influences which make a good student: the art of detachment, the virtue of method, the quality of thoroughness, and the grace of humility. In all these particulars Amberson qualifies.

I would like to emphasize that the word *student* as here used is far from being restricted to an undergraduate meaning. Once a man puts his hand to the medi-

cal plow, he is not fit for the Kingdom of Heaven unless he looks ever forward. To do so he must be a conscientious student. I earnestly counsel you to read the October, 1955, issue of the *International Record of Medicine and General Practice Clinics* which is entirely devoted to a Symposium on Medical Writing. Particularly, you must read the article by Felix Marti-Ibanez, the editor, on "Books in the Physician's Life." Here you will find much sound advice as well as information presented by a learned writer. Note what he has to say about *chronophages*, stealers of your valuable time. I have not recently refreshed my memory on the place, but somewhere it is recorded that Osler, while shaving in preparation for going out to dinner, always had his son Revere come into the bathroom armed with a designated book from which he would read aloud; thus Osler wasted no moments, refreshed his own memory, inculcated in his son the love of good literature, introduced him to the great men of bygone days, and at the same time cherished the father and son relationship, so precious and yet all too frequently neglected in a busy doctor's life.

In 1902, Henry Barton Jacobs (1858–1939) of Baltimore wrote a paper of great historical interest on "Some Distinguished American Students of Tuberculosis." You will find it in the Johns Hopkins Bulletin for August–September of that year. I refer to it here because a moment ago I said that, as Laennec was the man of the hour, and Trudeau to his generation, so was Amberson for our time and our special field. I should have said Laennec (1781–1826) and P. C. A. Louis (1787–1872) were the men of the hour, since, as Osler (1849–1919) and Jacobs pointed out, a small group of American doctors, shortly after their graduation, hastened to study in France under Laennec, Louis, Andral (1797–1876), A. J. Chomel (1788–1856), and J. N. Corvisart (1755–1821), and brought back from France to American medical schools auscultation and percussion, the new methods of diagnosis of chest diseases.

Of the half dozen men whose contributions to American medicine were reviewed by Jacobs, the most important in this connection were Samuel George Morton (1799–1851), James Jackson, Jr. (1810–1835), William W. Gerhard (1809–1872), and Henry Ingersoll Bowditch (1808–1892). Benjamin Rush (1745–1813) somewhat antedated this French school. He falls among that other earlier group of Americans who studied at Edinburgh. Austin Flint (1812–1886) was too busy changing his American scene of operations from Northampton to Boston to Buffalo to Chicago to Louisville to Buffalo to New Orleans to final settlement in New York as Professor of Medicine at Bellevue Hospital Medical College and Physician to Bellevue Hospital to spend much time overseas.

Jacobs says of Flint "His habits were simple, his manner polished; independent and fearless in his opinions; of sterling integrity and spotless in character. No one could come in contact with him without feelings of respect, confidence and love."

He could have been speaking of Amberson! His professional interest was particularly drawn to the physical signs of diseases of the chest and especially to those "refinements of auscultatory phenomena which admit of differentiating fine pathological distinctions." Jacobs promptly recognized the importance of

Villemins' (1827–1892) demonstration (1865) of the infectiousness of tuberculosis, Koch's (1843–1910) proof (1882) of the tubercle bacillus as the agent of infection, and he was a vigorous supporter of the diagnostic methods and clinical conceptions of Laennec and Louis. You recall Villemins' prescient words to his aides at Val de Grace "the phthisical soldier is to his messmate what the glandered horse is to its yokefellow."

Other important American doctors who studied in Paris and returned to infuse new life into American medical schools were Oliver Wendell Holmes (1809–1894) and George Cheyne Shattuck (1813–1893) of Boston, Alfred Stille (1813–1900) and William Pepper (1843–1898) of Philadelphia, William Power (1813–1852) of Baltimore. The latter died shortly of tuberculosis but lived long enough to teach "clearly and impressively the glorious discoveries of Laennec" (Packard).

You will recall that, in 1843 in his clinic in Paris, Trousseau (1801–1867) was doing thoracentesis for pleural effusion and that Clifford Allbutt (1836–1925) took this method of treating pleural effusion back to England in the same year. The first recorded aspiration of pleural fluid in America was done by Morrill Wyman (1812–1903) on February 23, 1850, and Henry Ingersoll Bowditch followed on April 7, 1850. To Bowditch is due great credit for demonstrating the safety and importance of aspiration of fluid from the chest. See his report in the *American Journal of Medical Sciences* for April, 1852, of 25 cases so treated.

I have in my library a reprint from *The Transactions*[4] *of the American Climatological Association* for June, 1889. It is an address by Henry I. Bowditch entitled "Open-air Travel as a Cure and Preventer of Consumption, as seen in the history of a New England family." The reprint is autographed "J. S. Billings, M.D., from his old friend, H.I.B.", and rubber stamped "Dr. J. S. Billings."

I quote the first paragraph:

> It is a curious coincidence that, at the same meeting of the Climatological Association, the President[5] should give you some information gleaned from my recorded cases as to the connection of pleurisy with phthisis, and I should present the history of my father, cured, as I believe, of severe phthisical symptoms by a journey in an open chaise, and by persistent daily walking of from five to six miles during the rest of his life. In connection with this I shall endeavor to show that, by the same persistent open-air treatment of his children during their periods of growth, he was able to prevent the recurrence of the same disease in a large number of his descendants, who, in consequence of himself and his wife being tuberculous, and also first cousins, must have been strongly *predisposed* to it.

Henry has a record of this journey as kept by his father in 1808, when he was thirty-five years of age. He says: "To some sensitive minds it may seem of too private and personal a character to be placed thus freely before any public assembly." But, he adds: "I have no such feeling when questions of human health and happiness are concerned."

[4] Of twenty-two papers read in the year 1889, 13 related to climatic influences on phthisis. O Tempora! O Mores!

[5] Vincent Y. Bowditch, son of Henry I. Bowditch, grandson of Nathaniel Bowditch.

In 1808, Nathaniel Bowditch[6] without much doubt had symptoms of pulmonary tuberculosis. He had cough, spitting of blood, anorexia, fever, and great debility. On August 29 of that year, "when thus ill," he started with a friend as his companion and driver in an open one-horse chaise for a tour through New England. (One of the earliest well-authenticated histories of "chaise-ing" the cure.) In reviewing the record of the journey, Henry showed to the Climatological Association a large map on which N.B. had marked with circles the towns where the nights were passed. "These circles were entirely black at first, indicating great depression of mind and body, and they became gradually lighter as the patient got better. Those over the last half of the journey were not only free from any shade, but were surrounded by a red border, indicating the comfortable feeling of returning health."

In brief, the traveler went from Salem, Massachusetts, down into Rhode Island, thence by way of Connecticut up through the hills of Western Massachusetts to Albany and Troy, back through Massachusetts to New Hampshire, Vermont, and Maine, and then to the home from which he started. During the trip he traveled 748 miles and passed through one hundred thirteen towns. "The time spent in this daily open-air exercise was thirty days. During that time he went through all stages of feeling of mental discouragement and of physical weakness up to a real enjoyment of life."

According to family tradition—it is not so recorded in the journal—he was much exhausted at the end of the first day and spit blood. The landlord of the hotel where they spent the first night advised Nathaniel's friend to "take him home to die." Despite continued fever and occasional hemoptysis, the journey was continued with almost steady improvement in the patient.

At New Haven, 256 miles from Salem and after twelve days of travel, he called on President Timothy Dwight of Yale College and regretted that the eminent Professor Benjamin Silliman (1779–1864), first Professor of Chemistry and Natural History at Yale, was absent. I am mortified to find that he visited the Yale library and "finds it wanting in most of the modern English, French and German scientific works he had been so long acquainted with, and had studied in Salem." Now Henry,[7] writing in 1889, admits that "the journey though benefiting him (Nathaniel) immensely, had not wholly cured him; but it had proved to him the absolute needs of regular, daily, physical, open-air exercise. Afterward under walks of one and a half to two miles, taken three times daily during thirty years of life, all pulmonary trouble disappeared. He died in 1838 from carcinoma of the stomach, one lung presenting evidences of an ancient

[6] Nathaniel Bowditch (1773–1838), mathematician and translator of LaPlace's *La Mecanique Celeste*. His life, written by his son Nathaniel Ingersoll Bowditch, was prefixed to the fourth volume (1839) of the translation of LaPlace.

[7] Henry Ingersoll Bowditch (1808–1893), one of the founders of the Boston Society of Medical Observation, which later became The Boston Society for Medical Improvement and led to the organization of the Boston Medical Library Association (1874). His little book *The Young Stethoscopist* (1846) did much to stimulate interest in auscultation in the United States. He was influential in organizing the ambulance service during the Civil War. His *Life and Correspondence* was written by his son, Vincent Y. Bowditch (1851–1929).

cicatrix at its apex, being otherwise normal. He was sixty-five years old—i.e., thirty years after the journey."

Henry now goes on to point out the risk of phthisis in the family. "My father," he says, "married his cousin, who, after long invalidism, died of chronic phthisis in 1834. Certainly a consanguineous union of two consumptives foreboded nothing but evil. They had eight children (born respectively in the years 1805, 1806, 1808, 1809, 1813, 1816, 1819, 1823)." In 1889 the number of descendants amounted to 93, 8 children, 31 grandchildren, 50 great-grandchildren, 4 great-great-grandchildren. Two children died, one at birth (1813) and the child born in 1809 died in 1820 at the age of eleven years, cause not stated. "Not a trace of phthisis has appeared in any of these 93 persons."

All this is to emphasize the important contributions of French physicians to American medicine and specifically to the knowledge and teaching of diseases of the chest.

* * *

I do not have to review the important part played by Trudeau in the sanatorium movement. That is well known. There remains my opinion of Amberson as the man of the hour in the years just past. I state my case with confidence that you will agree. Since the organization of the National Tuberculosis Association and the nation-wide campaign for control of this disease, the prime purpose of all of those associated with this movement has been to teach Dr. Dits (the Doc in the street) how to diagnose tuberculosis early, how to prevent its spread, how to treat it. Amberson's influence has extended far beyond the wards of Bellevue Hospital, directly and indirectly. His wisdom has permeated Metropolitan New York and the State of New York, it has influenced military decisions for the recognition and control of tuberculosis, it has indirectly spread over the United States and foreign countries through the instruction and training of young doctors. Magnificent as all this has been, it would not have earned for him the conspicuous evidences of affection of his students, if it had not been accompanied by the example he has unobtrusively set of the kindly physician.

By indirection, I shall try to give you my meaning. In a foreword to a special edition of Ian Maclaren's *A Doctor of the Old School*, Alexander Woollcott said: "I am aware that when I meet some one who has not read this book I not only pity him but do not quite like him." On re-reading that chapter called "The Mourning of the Glen" or the one wherein Dr. MacLure and his mare, Jess, bring the great Edinburgh surgeon through the flood to save the life of Tammas Mitchell's Annie, Woollcott said he felt that all of his journalistic days had been wasted and that he might better have spent his time going from house to house with a wheel-barrow full of copies of *A Doctor of the Old School*.

In yet another reprint of *A Doctor of the Old School*,[5] I find a preface by Ian Maclaren himself, in which he answers an oft-repeated question, "Was there ever any doctor so self-forgetful and so utterly christian as William MacLure?' To which he answers:

> Not one man, but many in Scotland and in the South country. I will dare prophecy also across the sea. It has been one man's good fortune to know four country

[5] Dodd, Mead & Co., 1897.

doctors, not one of which was without his faults—Weelum was not perfect—but who, each one, might have sat for my hero. Three are now resting from their labors, and the fourth, if he ever should see these lines, would never identify himself.

From all parts of the English-speaking world letters have come in commendation of Weelum MacLure, and many were from doctors who had received new courage. It is surely more honor than a new writer could ever have deserved to receive the approbation of a profession whose charity puts us all to shame.

May I take this first opportunity to declare how deeply my heart has been touched by the favor shown to a simple book by the American people, and to express my hope that one day it may be given me to see you face to face.

John Watson, whose pseudonym was Ian Maclaren, was a Scottish author and minister born in 1850 and died in 1907 while on a visit to America. *A Doctor of the Old School* was merely a part of *Beside the Bonnie Brier Bush*, a best seller of the middle Nineties and, to quote "Alex" again, 'One saw it in the hand of every Gibson Girl, and found it, in its gray-green cover, left in every hammock and deck-chair from Kansas City to Port Said."

Note that William MacLure, the "Doctor of the Old School," was a country doctor and so were the other four like him mentioned by Ian Maclaren. I humbly suggest that a "Doctor of the New School" has taught and practiced medicine in a metropolitan environment with the same humility and humanitarian spirit as Ian Maclaren's "Doctor of the Old School."

(Dr. Waring then handed Dr. Amberson a copy of "Beside the Bonnie Brier Bush" with the following statement:)

"This modest copy of *Beside the Bonnie Brier Bush*, which contains the famous story of *A Doctor of the Old School*, is presented to Dr. J. Burns Amberson, Jr., who by his life and works has instilled into many generations of young doctors in a metropolitan hospital environment the wisdom, humility, and dedicated spirit of *A Doctor of the Old School*."

CLINICOPATHOLOGIC STUDY OF TUBERCULOUS MENINGITIS IN ADULTS[1, 2]

HELENA E. RIGGS, CHARLES RUPP, AND HOMER RAY

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INTRODUCTION

Despite intensive preventive measures to detect tuberculosis in its incipient stages and increasingly effective therapy, spread of infection to the nervous system continues to be of serious import. Particularly is this true of adults in whom untreated tuberculous meningitis is almost invariably fatal. An obstacle to successful management is the infrequency of this disease in older persons and a consequent dearth of information concerning the distribution of tuberculous infection in such persons. It is thought that an analysis of a series of clinical and necropsy records may offer a more inclusive concept of the nature and extent of the underlying pathologic process in adults who develop meningeal complications, and may thus provide a more rational basis for therapy.

At the Philadelphia General Hospital where, between 1935 and 1954, inclusive, 3,549 necropsies were performed on patients with active tuberculosis, meningeal extension was present in 19.3 per cent of all tuberculous patients less than twenty years of age, and in 5.9 per cent of those older than twenty years. This study is based upon 185 persons comprising the adult group. All ages from twenty to more than seventy were represented; 46 per cent were forty years of age or older.

The age distribution of the patients is shown in table 1.

OBSERVATIONS

Clinical Features

Unawareness of the presence of tuberculous infection and delay in initiating treatment, once meningeal complications have occurred, was at once apparent as a definite factor in therapeutic failure. Meningitis as a terminal phase in patients already hospitalized for tuberculosis accounted for only 25 per cent of adults with meningitis. A history of previous treatment was obtained in 29, but none of these had had recent medical observation. Symptoms suggestive of active infection, such as loss of weight, cough, and night sweats, in many instances preceded signs of meningeal spread. Very frequently, however, medical advice was deferred until the meningeal process was well advanced. Forty (21 per cent) of the patients were admitted to the hospital in coma or with signs of rapidly increasing intracranial pressure, and succumbed within a few days after arrival.

A fulminating course in some patients precluded successful outcome. Nevertheless, at least one-third of the group had noted premonitory symptoms, such as

[1] From the Philadelphia General Hospital, Philadelphia, Pennsylvania.

[2] Presented at the Joint Meeting of the Philadelphia and New York Neurological Societies, Philadelphia, Pennsylvania, April 6, 1956.

TABLE 1

CLINICOPATHOLOGIC STUDY OF TUBERCULOUS MENINGITIS IN ADULTS
Age Distribution

Age by decades	20	30	40	50	60	70
All forms of tuberculosis	723	635	658	546	387	155
Tuberculous meningitis	57	43	45	30	9	1
Per cent complicated by meningitis	7	7	7	5	2.5	0.6

headache, neck pain, and vomiting from one to three weeks prior to admission. Prior to the development of frank meningeal irritation, mental disturbances (such as confusion, lethargy, personality or behavior changes) were present in 33 patients. While the neurologic manifestations were predominantly those of meningeal irritation and increased intracranial pressure, focal signs due to intracerebral tuberculomata complicated the clinical picture in 20 cases and in some instances preceded or overshadowed the presence of meningitis.

Pathologic Observations

Tuberculous infection of the meninges in adults was found to constitute merely one aspect of a widely disseminated process. Active, well-established tuberculous foci were present in 165 (86 per cent), in extraneural systems, brain parenchyma, or both. Acute miliary spread of infection was superimposed in 100 (61 per cent) and was present in 14 in whom no locus of chronic disease was detected. In 6 cases, the origin of the meningeal infection was not found at necropsy.

Chronic tuberculous activity was not confined to any particular organ or system. The location of the tuberculous foci is shown in table 2.

The process was limited to the lungs in 54 patients, and to extrapulmonary structures in 67. Forty per cent of the patients had active tuberculous lesions in more than one system. Chronic pulmonary infection was present in 98 cases; and caseous foci in abdominal organs, chiefly the adrenal and genitourinary systems, were found in 45. Lymph node tuberculosis was present in 27 and was the only locus of chronic infection in 14 patients. The abdominal and thoracic chains were chiefly implicated, while cervical adenitis was present in 5 patients. Skeletal tuberculosis was found in 14 patients, 7 of whom showed no other chronic focus.

It is of particular interest that the brain was more frequently the site of chronic tuberculous foci than any organ except the lung. Cerebral tuberculomata are considered to be associated predominantly with childhood infection, but they were found in 36 per cent of the adults who died with tuberculous meningitis and in only 20 per cent of the children. Fifty-two patients with intracerebral granulomata also presented foci of chronic tuberculosis in extraneural structures. Tuberculomata were the only manifestations of chronic infection in 7 patients, 3 of whom showed an acute hematogenous spread in addition to involvement of the meninges.

Tuberculomata were frequently widely disseminated throughout the nervous

TABLE 2

LOCATION OF FOCI IN CHRONIC ACTIVE TUBERCULOSIS

(165 Adults)

	Tuberculosis Limited to Single System	Multiple-System Involvement	Total
Lung	54	44	98
Brain parenchyma	7	52	59
Lymph nodes	14	13	27
Adrenal	9	12	21
Genitourinary	5	13	18
Skeleton	7	7	14
Others	3	3	6

system, but in 24 instances only a solitary focus was present. Sites of predilection were the hemispheres and the cerebellum, although no part of the central nervous system was entirely spared. In view of Rich's (1) concepts of the pathogenesis of tuberculous infection of the meninges, it is of interest that the lesions in 53 patients were adjacent to the subarachnoid space or the ventricular system and, in some instances, were actually embedded in the choroid plexus or ependyma. While the size and the degree of surrounding fibroglial reaction suggested that the cerebral tuberculomata may have been present for a relatively long period, in some cases it was possible to stain tubercle bacilli in apparently well-encapsulated and quiescent lesions.

DISCUSSION

This analysis is undoubtedly influenced by racial and socio-economic factors inherent in the case material from which it is drawn. The Philadelphia General Hospital is a charity institution in a metropolitan area where the incidence of tuberculosis is high, especially among Negroes. Seventy-nine per cent of necropsied tuberculous patients in this hospital are Negroes. Racial susceptibility is reflected in the number of Negroes (80 per cent) included in this study. Numerical disproportion is counteracted by the fact that the incidence of meningeal complications was no higher in Negro than in white patients. Meningitis in both racial groups was associated, in relatively the same degree, with chronic activity in distant organ foci and with terminal hematogenous dissemination. Chronic tuberculous involvement of the lymphatic system, however, was found almost exclusively in the Negro.

The report of Auerbach (2), based upon necropsy studies of 67 adults with meningeal tuberculosis and drawn from much the same type of case material, is in general agreement with the present findings. As in the present series, Auerbach found that meningeal complications were associated with active foci in the lung and extrapulmonary systems, and in a high percentage were complicated by acute hematogenous spread. But, even with the relatively homogenous representation in these two groups, certain differences were apparent. Meningeal tuberculosis in Auerbach's patients was correlated in 75 per cent with foci in the skeleton and

genitourinary organs, whereas, in the present study, infection in these locations was found in only 19 per cent and was limited to one or both systems in 13 per cent.

In both Auerbach's and the present cases, the high incidence of disease in Negroes may have influenced the conclusions and inferences drawn from these studies and may require modification in the light of the manifestations of tuberculosis in other population groups. The necessity for further accumulation of necropsy data, however, appears essential for adequate understanding and successful treatment of adults who develop this grave complication. This fact is emphasized in view of the conflicting reports of cure of tuberculous meningitis in adults. Cairns (3) reports 50 per cent recovery in 60 patients of all ages except "the very young and very old." He modifies this statement, however, by noting that, except with prolonged therapy, results are poor in meningitis associated with miliary tuberculosis or with the adult type of pulmonary tuberculosis. In the same year, the U. S. Veterans Administration, reporting to the Council on Pharmacy and Chemistry of the American Medical Association (4), reported only a 15 per cent survival rate for 100 adults with "pure tuberculous meningitis" treated with streptomycin, and no survivors after two to three years among adults with miliary tuberculosis accompanied or followed by tuberculous meningitis. Such widely divergent results with similar therapeutic regimens suggest that the outcome may depend upon the type and extent of the tuberculous infection at the time of the meningeal complication.

The results of the present survey suggest that tuberculous meningitis in adults develops after the tuberculous infection has become firmly established and widely disseminated. Failure to recognize the presence of the disease in its early stages is not entirely related to the socio-economic strata of the patients. Necropsy records at this hospital show that, although the incidence of fatal tuberculosis in adults (10 per cent) has not altered during the twenty years covered by this study, the rate in children and adolescents has fallen from 22.2 per cent during the years 1935–1944 to 6.6 per cent in the decade 1945–1954. The location and nature of the tuberculous process at the time meningeal complications develop in adults point to prior hematogenous dissemination, following which organ metastases either fail to regress or become reactivated. With this pattern of infection it may be difficult to establish a diagnosis of tuberculosis, particularly if active foci are limited to extrapulmonary systems. Even after therapeutic arrest, reactivation may occur from foci in inaccessible or silent areas. Cure of meningeal complications in adults, therefore, may depend primarily upon prevention of extensive inroads of tuberculosis and aim at control of the disease before the development of meningeal infection.

SUMMARY

A clinicopathologic study of 185 cases of tuberculous meningitis in adults demonstrated that meningeal complications constituted only one aspect of a widely disseminated process. Active foci were found in extraneural systems, brain parenchyma, or both, in 86 per cent of the patients. Successful therapy

may depend primarily upon prevention of extensive inroads of tuberculosis and control of the disease before complications develop.

SUMARIO

Estudio Clínicopatológico de la Meningitis Tuberculosa en los Adultos

Un estudio clínico e histopatológico de 185 casos de meningitis tuberculosa en personas adultas demostró que las complicaciones meníngeas no constituían más que una fase de un proceso diseminado ampliamente. En 86 por ciento de los enfermos, encontráronse focos activos en los sistemas extraneurales o el parénquima cerebral, o en ambos. El éxito terapéutico puede depender primariamente de la prevención de incursiones extensas de parte de la tuberculosis y del dominio de la enfermedad antes de aparecer complicaciones.

RESUME

Etude clinico-pathologique de la méningite tuberculeuse chez l'adulte

Une étude de la pathologie clinique de 185 cas de méningite tuberculeuse chez l'adulte a démontré que les complications méningées ne constituaient qu'un seul des aspects d'un processus largement disséminé. Des foyers actifs furent découverts dans les systèmes extra-neuraux, le parenchyme cérébral ou les deux, chez 86 pour 100 des malades. Le succès du traitement peut dépendre au premier chef de la prévention de l'extension de la tuberculose et de la stabilisation de l'affection avant que les complications n'apparaissent.

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PNEUMOENCEPHALOGRAPHY IN TUBERCULOUS MENINGITIS[1,2]

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INTRODUCTION

Tuberculous meningitis was a universally fatal disease until the advent of streptomycin therapy. With streptomycin and the newer antituberculous drugs, mortality from this disease has been greatly reduced (1–3), but the mortality rate has remained significantly higher than that of tuberculosis of other organs. This fact in itself indicates that therapeutic factors other than the direct antimicrobial attack on the invading organisms are involved in the successful treatment of tuberculous meningitis.

Tuberculous meningitis in children rather frequently produces a severe basal leptomeningitis with resulting communicating hydrocephalus (3–5) which in some textbooks is stated to be characteristic of tuberculous meningitis (6). The use of parenteral and intrathecal streptomycin has not affected this complication significantly (7, 8), and streptomycin instillation directly into the basal cisterns by an inlying polyethylene catheter (2) has not prevented it. Statistically, such hydrocephalus in children is reported to occur in 22 to 63 per cent by autopsy study (9), and in 59 per cent by serial pneumoencephalographic studies (6). No reports deal with this complication in adults with tuberculous meningitis.

The higher mortality rate found in those patients with such an hydrocephalus (3, 10–12) is to be expected since increased intracranial pressure does result from the hydrocephalus (13, 14). The brain does not tolerate or resist infections well when under increased pressure (15). In addition, the increased intraventricular pressure itself causes certain profound deficits (12, 16) and may cause death.

Prevention of communicating hydrocephalus in tuberculous meningitis by early treatment has been strongly emphasized (9), but it is surprising to note that aggressive efforts to diagnose this complication early by roentgenographic studies have rarely been reported in this country although several reports have been presented in other countries (1, 2, 6, 17). Apparently as a direct result of this, little effort has been made here to treat adequately or control the hydrocephalus. The attitude that operation is not helpful in such cases (6) is difficult to accept since the increased pressure of communicating hydrocephalus due to other causes responds well to a variety of procedures (14, 18–21). Various methods of intermittent ventricular drainage by puncture (1), constant external drainage of the ventricles (2), and ventriculo-mastoid shunts have been used in other

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countries with reduction in mortality (2). There has apparently been only minimal effort in this country (21*a*), however, to treat the hydrocephalus and thus obtain maximal salvage of cerebral structures from the advancing infection as well as from the increased pressure.

In an effort to improve the treatment of tuberculous meningitis by early diagnosis and treatment of cerebral complications, a flexible program was set up at Firland Sanatorium four years ago with a twofold objective: to determine the type, frequency, and course of cerebral complications such as hydrocephalus both in adults and children by the early and repeated use of pneumoencephalography on all patients admitted with tuberculous meningitis; and to treat the increased intracranial pressure of communicating or obstructive hydrocephalus by operation as early as possible. The results of only the first objective are included in this initial report.

MATERIALS AND METHODS

Each of the 47 patients (22 adults, 25 children) admitted to the sanatorium with tuberculous meningitis was considered for pneumoencephalography only after the admission examination was completed and the diagnosis of tuberculous meningitis established by the history, neurologic examination, and the findings in the cerebrospinal fluid. Ultimately, tubercle bacilli were cultured from the cerebrospinal fluid in all cases. Chemotherapy, consisting of streptomycin and isoniazid-PAS, was started immediately in every case. The drug dosages varied, depending on the patient's age and the severity and type of the tuberculosis. Pneumoencephalography was carried out under Pentothal® anesthesia one to three weeks following admission provided that the neurologic evaluation indicated no significant mass lesion in the posterior fossa. In all instances except in the patients with advanced hydrocephalus, complete replacement of the cerebrospinal fluid by oxygen was attempted and persistent efforts were made to fill all of the cerebrospinal fluid spaces. In the acutely ill patients with papilledema, ventriculography under local anesthesia was done as soon as possible, often as an emergency measure. When indicated, ventriculo-mastoidostomy shunt operations were carried out after the diagnostic air studies were completed.

In all instances in which pneumoencephalographic abnormalities were believed to be progressive in nature, serial follow-up air studies were done at subsequent intervals of two to six months or as indicated by clinical deterioration or change. Such follow-up studies covered periods up to four and one-half years in certain instances. A total of eighty-two air studies was done on 45 patients, consisting of fifty-seven on 25 pediatric patients and twenty-five on 20 adult patients.

In cases in which ventricular enlargement was found on the air study, measurements of ventricle size were taken, as illustrated in figure 1*B*. If line 1, measuring the diagonal width of the lateral ventricles, is greater than 2.0 cm., ventricular dilatation is present (22). In the communicating hydrocephalus group, this measurement was used as an arbitrary means of classification into minimal (2.5–3.0 cm.), moderate (3.0–4.0 cm.), and advanced (4.0 cm. and greater) hydrocephalus.

Line 2 in figure 1*B* measures the width of the lateral ventricles, primarily anterior horns. This measurement incorporated in a ratio with the maximal internal diameter of the skull, known as Evan's Ratio (24, 25), has a normal value of 0.20–0.25, with a value of 0.30 or greater indicating enlargement. Initial use of this ratio was abandoned in favor of the simpler method of measuring line 1.

Line 3 in figure 1*B* measures the depth of the anterior horns of the lateral ventricle. This was measured in the lateral "brow-up" position, however, to avoid angulation error. Line 4 in figure 1*B* measures the width of the third ventricle. Lines 2, 3, and 4 were directly variable with each other in most cases of communicating hydrocephalus and, together with line 1,

were valuable in charting the variation and change in ventricle size shown in the serial air studies.

Repeated neurologic and cerebrospinal fluid examinations were done in order to estimate accurately the progress of therapy and in the hope of finding a typical, neurologic syndrome indicating communicating hydrocephalus (26).

All of the 20 adult patients were studied with pneumoencephalography during their first hospitalization for tuberculous meningitis. Two of the 25 pediatric patients were called back into the hospital after having been bacteriologically cured previously. The specific objective of rehospitalization was to obtain pneumoencephalography (*Cases 35* and *36*).

OBSERVATIONS

The results of the study consist primarily of the roentgenographic findings. Secondarily, the results emphasize the need of early and adequate cerebral air studies, since the neurologic and laboratory examinations frequently failed to give reliable indications of the true cerebral status.

In table 1 may be seen the roentgenographic findings of pneumoencephalography in the 20 cases in adults. Only one air study of the entire group was considered entirely normal, similar to the anteroposterior view illustrated in figure 5*A*.

Two adult patients had communicating hydrocephalus. In figure 1 are shown serial pneumoencephalograms on a 19-year-old white male (*Case 2*) who had been ill for three weeks prior to a pneumoencephalogram (figure 1*A*) done in an outside hospital. The cerebrospinal fluid removed at that study showed tubercle bacilli for the first time, and the patient was admitted to the sanatorium. One week after admission, the pneumoencephalogram in figure 1*B* showed symmetrically dilated ventricles, with no subarachnoid oxygen over the hemispheres and a block to oxygen at the basal cisterns, characteristic of communicating hydrocephalus (13, 14). The patient had progressing communicating hydrocephalus of moderate degree which required early ventriculo-mastoidostomy.

The other adult showing communicating hydrocephalus was a 23-year-old white female (*Case 10*). In figure 2*A* the anteroposterior view of her initial pneumoencephalogram is demonstrated. She had elevated cerebrospinal fluid pressure, and measurements showed ventricular enlargement although some subarachnoid oxygen was present over the hemispheres. This was a minimal

TABLE 1

PNEUMOENCEPHALOGRAPHIC FINDINGS IN CASES IN ADULTS

Entirely normal		1
Partial obliteration and dilatation of basal cisterns; otherwise normal		1
Communicating hydrocephalus		2
Minimal, arrested	1	
Moderate, progressive	1	
Ventricle asymmetry; otherwise normal		3
Cerebral atrophy		13
Generalized atrophy	9	
Generalized with ventricle shift	2	
Focal atrophy	2	

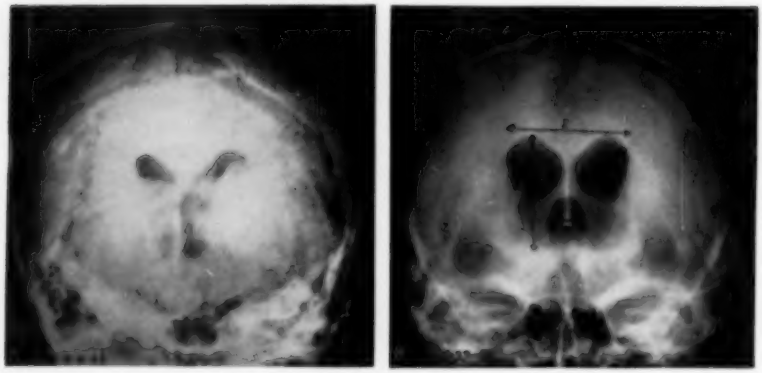

FIG. 1. *Case 2*, 19-year-old white male. *A*. Normal pneumoencephalogram one week prior to admission. *B*. Pneumoencephalogram one week after tuberculous meningitis shows communicating hydrocephalus.

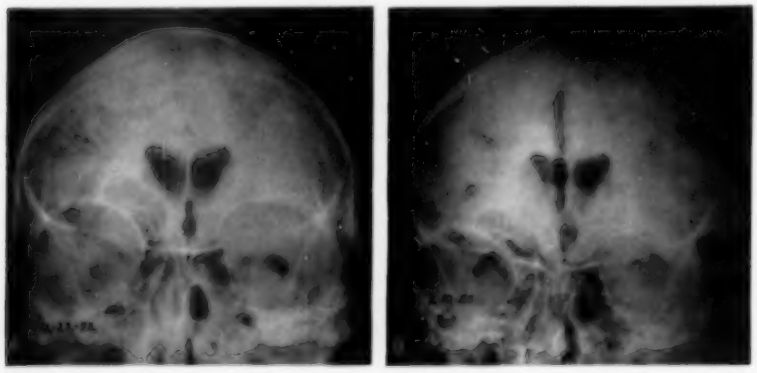

FIG. 2. *Case 10*, 23-year-old white female. *A*. Admission pneumoencephalogram showing early hydrocephalus by measurement, but significant subarachnoid air. *B*. Serial pneumoencephalogram two months later shows no progression of the hydrocephalus, possible resolution.

communicating hydrocephalus which was proved to be arrested, since the serial pneumoencephalogram in figure 2*B* showed no progression two months later.

In figure 3*A* may be seen the lateral "brow-up" view of the pneumoencephalogram in the single instance in which obliteration of the cisterna chiasmaticus and mild dilatation of upper cisterna pontis and ambiens was demonstrated, presumably secondary to exudative and adhesive tuberculous leptomeningitis. Obliteration of cerebrospinal fluid pathways was not extensive enough to cause a communicating hydrocephalus, since the ventricles and hemispheric subarachnoid spaces are normal in appearance. Serial air study showed no progression three months later.

The same view of a pneumoencephalogram in a 49-year-old man may be seen in figure 3*B*. This demonstrates excellent filling of all of the basal cisterns (27) as compared with figure 3*A*. Mild ventricular enlargement associated with abnormally large subarachnoid spaces over the hemispheres indicates generalized cerebral atrophy; 13 of the adult patients showed cerebral atrophy, 9 of them showing generalized cerebral atrophy in the anteroposterior view. The presence of focal cerebral atrophy, probably secondary to an old head injury and not related to the meningitis, may be seen in figure 4*B*. Two such cases were present.

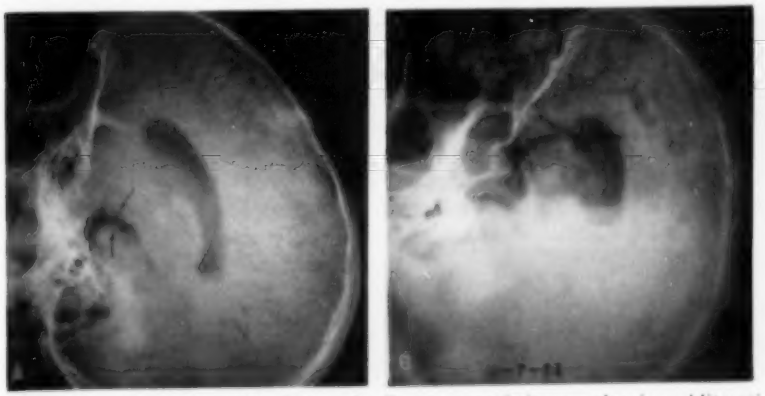

FIG. 3*A*. *Case 1*, 44-year-old white male. Pneumoencephalogram showing obliteration of basal cisterns at upper cisterna pontis (arrows) but normal ventricle size and presence of subarachnoid oxygen. No change on follow-up studies. *B*. *Case 6*, 49-year-old white male. Same pneumoencephalogram view for comparison with *A*, showing large cisterna chiasmatica and interpeduncularis associated with general cerebral atrophy.

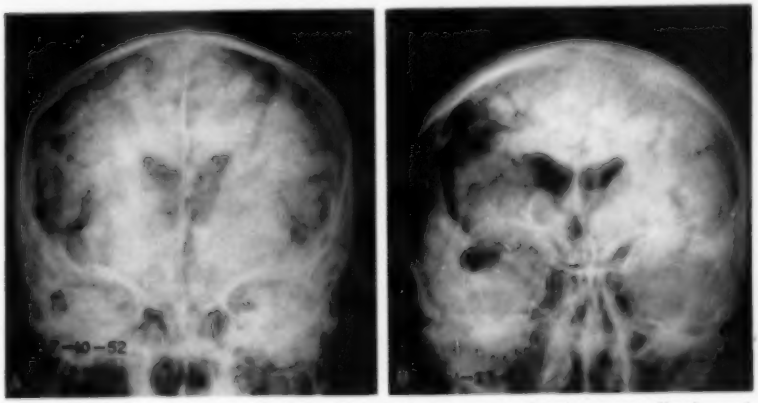

FIG. 4*A*. *Case 7*, 45-year-old white male. Admission study showing generalized cerebral atrophy with huge subarachnoid spaces over the hemispheres. *B*. *Case 8*, 47-year-old white male. Admission study showing localized cerebral atrophy, right parietal lobe.

TABLE 2

PNEUMOENCEPHALOGRAPHIC FINDINGS IN PEDIATRIC CASES

Communicating hydrocephalus		17
Advanced in degree	7	
Moderate in degree	8	
Associated aqueduct block	1	
Minimal in degree	2	
Normal		2
Dilated basal cisterns; normal otherwise		3
Generalized cerebral atrophy		3

Abnormal pneumoencephalograms were present in 19 of the 20 adult patients, but the abnormalities on the whole were not necessarily related to the tuberculous meningitis. It is probable that there would have been very similar findings if cases of pulmonary tuberculosis only had been investigated, with the exception of the 2 cases of hydrocephalus and the one basal leptomeningitis. The findings otherwise seem to be more characteristic of the age group and socioeconomic class of adults who have had the average number of head injuries and illnesses. The possible role of tuberculous arteritis in these cases is not known.

The pneumoencephalographic findings in the pediatric patients (six months to fifteen years of age) are presented in table 2. The results are strikingly different from those in the adult group. A communicating hydrocephalus was present in 17 (68 per cent) of the 25 patients and could be classified as advanced in 7 patients, moderate in 8, and minimal in 2 patients. Two patients showed normal studies and 3 showed partially obstructed, and therefore dilated, basal cisterns without other abnormality. Three patients had generalized cerebral atrophy similar to that presented in figure 4*A*.

A normal-appearing pneumoencephalogram in the anteroposterior view is presented in figure 5*A*. The lateral view in figure 5*B*, however, shows the partially obstructed and dilated basal cisterns, as outlined by the arrows. The mild degree of basal leptomeningitis which had caused this condition was not severe enough to impair significantly the cerebrospinal fluid flow through the cisterns to the hemispheric subarachnoid spaces, and no hydrocephalus resulted. Two similar cases likewise showed no progression on serial pneumoencephalography.

One of the 7 cases of far advanced communicating hydrocephalus in an infant may be seen in figure 6*A*. Huge ventricles are present and a block to the subarachnoid oxygen at upper cisterna pontis (arrows) and separated skull suture lines may be seen. In another infant patient (figure 6*B*), the pneumoencephalogram shows huge ventricles and complete block to oxygen at the cisterna interpeduncularis and chiasmaticus (arrows). All in this group were desperately ill during progression of the hydrocephalus and even the survivors were seriously crippled from the neurologic standpoint. Only the patient of *Case 45* represented an exception to this course (table 3).

In figure 7, serial air studies of an infant with advanced communicating hydrocephalus on the initial air study (figure 7*A* and *B*) revealed marked reduction

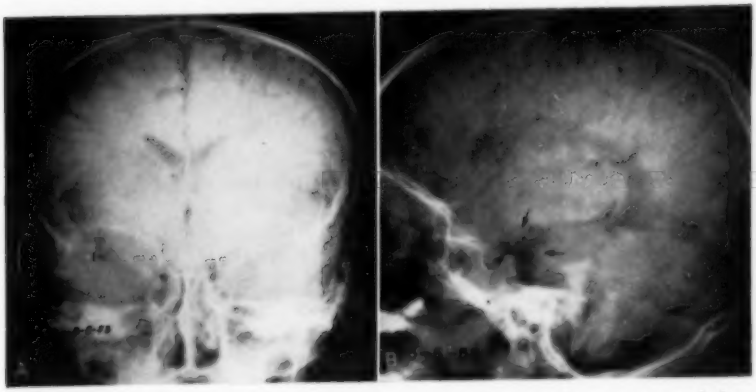

FIG. 5. *Case 45*, 5-year-old white female. *A*. Apparently normal pneumoencephalogram in anteroposterior view. *B*. Lateral view shows ballooned basal cisterns (arrows) of marked degree, but is normal otherwise.

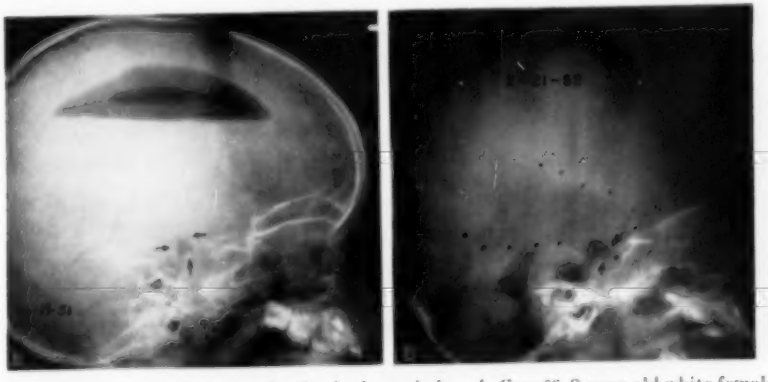

FIG. 6. Far advanced communicating hydrocephalus. *A*. *Case 26*, 2-year-old white female. Basal cistern block at upper cisterna pontis (arrows), separation of skull sutures, huge ventricles *B*. *Case 38*, one-year-old Indian female. Basal cistern block at cisterna interpeduncularis and chiasmaticus, huge temporal horn (dots), and very large fourth ventricle and cisterna magna.

in ventricle size two years later (figure 7*C* and *D*) after ventriculo-mastoid shunt. The block to oxygen in the basal cisterns was still present (arrows, figure 7*D*), but the hydrocephalus was arrested and was no longer associated with high intracranial pressure.

A moderate communicating hydrocephalus is demonstrated in figure 8*A* in which moderate ventricular enlargement was associated with minimal subarachnoid oxygen over the hemispheres and separation of skull sutures. Ten months after ventriculo-mastoid shunt, the resolution of ventricular enlargement and control of the intracranial pressure was shown by closure of the skull sutures

TABLE 3

PEDIATRIC CASES

Patient Number	Age	Interval from Onset to Treatment	Interval from Onset to Diagnostic Air Study	Associated Spinal Disease	Operation	Result; Time Since Onset
Advanced hydrocephalus (7):						
24, M.C.	5½ years	28 days	6 weeks	0	Craniotomy, shunt	Died; 11 months
25, M.C.	1½	12 days	6 weeks	L1 block	Shunts	Blind, deaf; 4½ years
26, L.G.	2	17 days	4 weeks	0	Shunt	Died; 5 months
28, L.I.	1½	7 days	1 year	0	0	Died; 1 year
30, D.K.	1½	28 days	3 months	0	0	Died; 2¼ years
38, A.R.	1½	8 days	6 months	0	0	Died; 4¾ years
45, R.L.	4¾	12 days	2½ weeks	0	Shunt	Almost normal; 7 months
Moderate hydrocephalus (8):						
27, M.H.	4	18 days	3½ weeks	0	Craniotomy, shunt	Near normal; 4 years
29, W.J.	3½	10 days	5 weeks	T12; L1	Shunt	Near normal; 4½ years
34, T.H.	1¾	10 days	8 weeks	0	Shunt	Mentally dull; 2 years
36, W.O.	6	22 days	2 years	0	0	Normal; 5¼ years
39, B.R.	4¾	14 days	2½ weeks	0	Shunt	Died; 4 months
43, J.O.	11	7 days	8 weeks	0	Shunt	Normal; 1¼ years
44, K.A.	3¾	28 days	4 weeks	0	Shunt	Died; 2 months
42, M.W.	6 months	21 days	2 years	0	0	Died; 3½ years
Minimal hydrocephalus (2):						
32, W.M.	10	21 days	6 weeks	0	Shunts	Near normal; 4½ years
41, M.W.	4¾	28 weeks	10 months	0	0	Near normal; 1½ years
No hydrocephalus (8):						
21, J.A.	10 months	21 days	5 weeks	0	0	Normal; 2½ years
22, J.B.	7	7 days	6 weeks	0	0	Normal; 2¾ years
23, E.A.B.	1¼	7 days	5 weeks	0	0	Near normal; 3 years
31, L.L.	4 months	21 days	3½ weeks	0	0	Normal; 3½ years
33, G.L.	5	7 days	3 weeks	L1	0	Near normal; 1½ years
35, J.O.	3½	4 days	1½ years	0	0	Normal; 5 years
37, D.L.	3¾	25 days	5 weeks	0	0	Normal; 2¼ years
40, C.S.	2¼	21 days	2 years	0	0	Normal; 4½ years

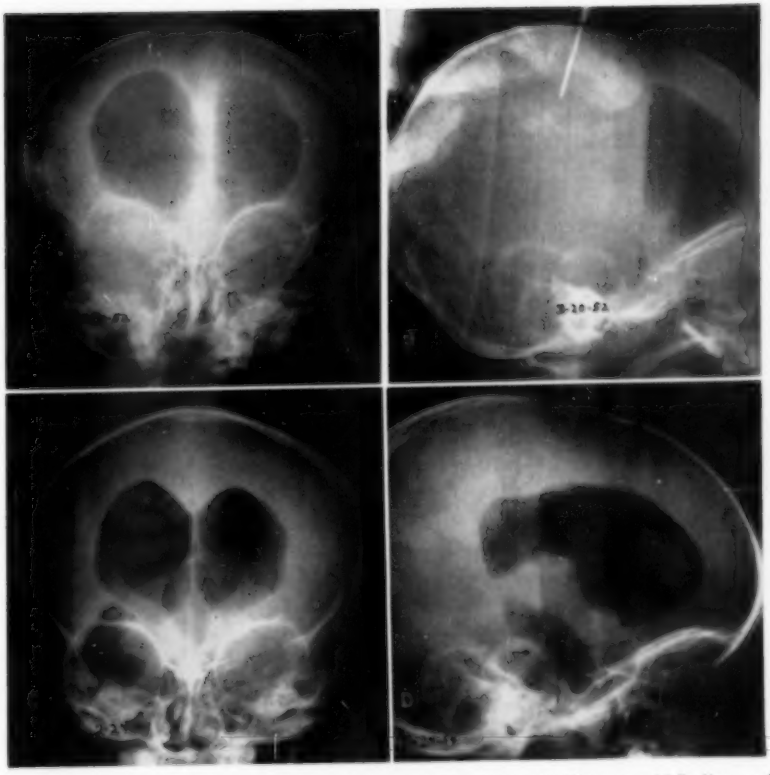

FIG. 7. Far advanced communicating hydrocephalus. *Case 25*, 1½-year-old Indian male. *A* and *B*. Tremendous ventricular enlargement with skull suture separation, desperate clinical status, on ventricular drainage. Ventriculo-mastoid shunt performed. *C* and *D*. Anteroposterior view and lateral view pneumoencephalograms obtained two years later show marked reduction in ventricular size, but persisting block to oxygen in basal cisterns (arrows).

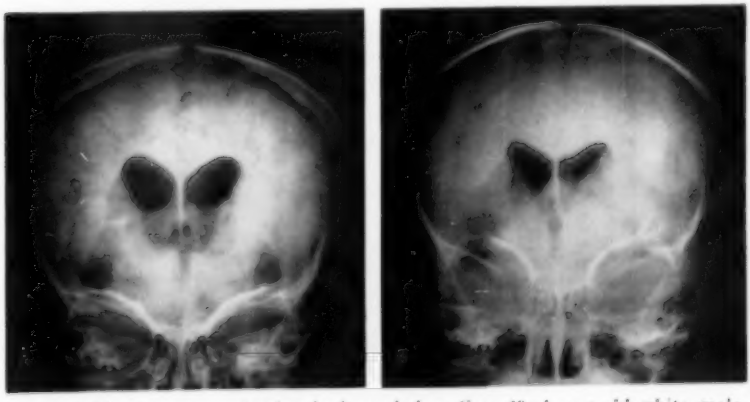

FIG. 8. Moderate communicating hydrocephalus. *Case 29*, 4-year-old white male. *A*. Pneumoencephalogram one month after meningitis onset shows moderately enlarged ventricles, suture separation, very little subarachnoid oxygen. *B*. Ten months after ventriculo-mastoid shunt, resolution of hydrocephalus generally, although focal enlargement of right temporal horn; suture closure.

(figure 8*B*). Focal dilatation of the right temporal horn had appeared, presumably secondary to vascular changes of a tuberculous endarteritis.

Eight pediatric patients showed a moderate communicating hydrocephalus. The diagnosis of the hydrocephalus was not established in 2 of them until two years after onset of the meningitis (table 3). In one of these patients the process remained arrested and nonprogressing (figure 9), but in the other it showed de-

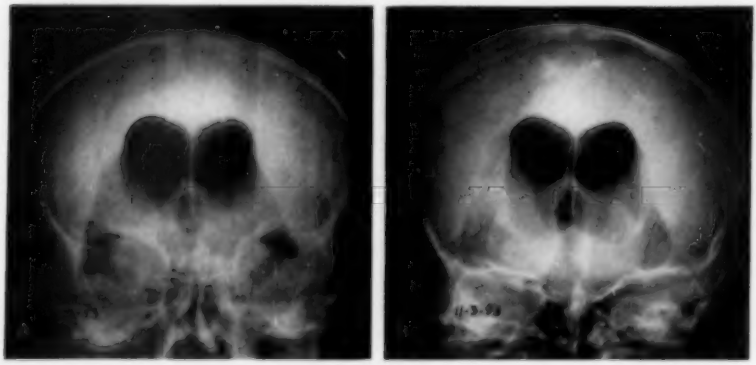

FIG. 9. Moderate communicating hydrocephalus, spontaneously arrested. *Case 36*, 7-year-old white male. *A*. Pneumoencephalogram two years after onset of meningitis; cerebrospinal fluid, normal for twenty months. *B*. Repeat pneumoencephalogram nine months later shows minimal resolution of ventricle size.

FIG. 10. Minimal communicating hydrocephalus. *Case 32*, 10-year-old white male. Early but definite ventricular enlargement with minimal subarachnoid oxygen over the hemisphere.

FIG. 11. Moderate communicating hydrocephalus with invagination of third ventricle floor by basal cistern exudate mass. *Case 34*, 1½-year-old white male. *A* and *B*. Antero-posterior and lateral views of pneumoencephalogram show enlarged fourth ventricle (dots), and block to oxygen at cisterna pontis (arrows). *C*. Brow-up lateral view shows invaginated floor of third ventricle (dots) by mass in cisterna chiasmaticus, block to oxygen at posterior cisterna chiasmaticus (arrows), separated sutures. *D*. Six months after ventriculo-mastoid shunt, only change is closure of the skull sutures and minimal reduction of hydrocephalus.

layed progression and caused death three and one-half years after onset of the meningitis (figure 12). In figure 9*A* the moderate hydrocephalus in the former patient is demonstrated and in figure 9*B* may be seen the serial study nine months later, with little change.

Two of the cases of communicating hydrocephalus were minimal in degree by measurement. In one case the process was spontaneously arrested, as proved by serial encephalography; but in the other patient it was progressive and required a ventriculo-mastoid shunt. In figure 10 may be seen the initial encephalogram in the latter case, showing minimal but definite ventricular enlargement associated with a block to oxygen in the basal cisterns with no hemispheric subarachnoid oxygen. The early diagnosis of the hydrocephalus in this patient

allowed early treatment, with a good clinical result in spite of a delayed, secondary progression (table 5).

The seriousness of associated hydrocephalus in children with tuberculous meningitis is quite evident since all of the 8 deaths were in the group with advanced or moderate communicating hydrocephalus (table 3). This is in accord with previous observations (6, 9, 11) and further supports the prognostic value of pneumoencephalography (7). Prevention of this degree of hydrocephalus would seem to be the logical approach.

By post-mortem observations, Lincoln (9) believed there was a correlation between the presence of hydrocephalus and the delay in active therapy at the

FIG. 12. Moderate communicating hydrocephalus progressing to death three and one-half years after apparent cure. *Case 42*, 7-month-old white male. *A* and *B*. Anteroposterior and lateral views of pneumoencephalogram one year and eleven months after onset of infection; moderately dilated ventricles with oxygen block at basal cisterns, early suture separation. *C* and *D*. Anteroposterior and lateral views of pneumoencephalogram ten months later show marked progression of hydrocephalus. Death from high intracranial pressure three months later; cerebrospinal fluid remained normal.

FIG. 13. Delayed hydrocephalus with block appearing in the aqueduct and the basal cisterns two years after meningitis onset, cerebrospinal fluid was normal for eighteen months. *Case 27*, 4-year-old white male. *A*. Anteroposterior view of initial pneumoencephalogram—slight ventricular enlargement with good subarachnoid oxygen over the hemispheres. *B*. Fourteen months later, progressing hydrocephalus apparent, but clinical status satisfactory. *C*. Pneumoencephalogram two years after onset (deteriorating clinically) shows block to oxygen at the aqueduct (crosses) with normal-size fourth ventricle, and block to oxygen in the basal cisterns (arrows). *D*. Ventriculogram immediately following *C* shows dilatation of ventricles. Torkildsen by-pass not completely effective, but ventriculo-mastoid shunt life saving.

onset of the disease. In table 3 may be seen the time interval between the onset of meningitis symptoms and the institution of active antimicrobial therapy in all of the pediatric patients, divided into those with and those without hydrocephalus. The average time interval for each of those groups was:

Advanced hydrocephalus	16 days
Moderate hydrocephalus	16 days
Minimal hydrocephalus	21 days (only one case included)
No hydrocephalus present	16 days

In this series, there is no immediate reason to believe that this time interval of delay in treatment has any relationship to the degree or even presence of hydrocephalus, since all patients received essentially similar initial therapy and had essentially the same period of delay between onset and treatment. In the adult patients, on the other hand, the interval from onset of meningitis to therapy ranged from four to twenty-eight days, and the average interval for the entire group was fourteen days. This probably has little significance with respect to the low incidence of hydrocephalus in the adults.

The interval between the onset of the disease and the diagnostic air study may give some rough idea of how rapidly the hydrocephalus developed, but this time interval is probably entirely too long, since the hydrocephalus must have been present for some time prior to the air study in almost all cases. The 5 cases with an interval of more than one year were patients treated prior to the start of the project, or treated elsewhere initially.

In table 3 it may be seen that only 3 of the 25 patients had obvious associated spinal disease, 2 of these having an arachnoiditis with partial block to cerebrospinal fluid and very high cerebrospinal fluid protein (*Cases 25* and *33*) and one having a bony lesion only (*Case 29*).

The duration of follow-up in the surviving patients varies from seven months to five years. All cases are still being followed carefully, either in the hospital or on an outpatient basis.

The fact that deaths occurred only in those patients with hydrocephalus indicates that early recognition of such hydrocephalus is probably very important. In table 4 are tabulated some of the signs and symptoms which might be of value in early recognition of hydrocephalus. In the experience of the writers, these do not form a clean-cut "hydrocephalic syndrome" (26). However, the advanced and moderate hydrocephalics all showed some evidence of brain-stem deficits at the time of their diagnostic air study. These signs varied from nystagmus through cranial nerve paresis to decerebrate responses as indicated. Very few of the nonhydrocephalics showed such signs. Such brain-stem signs are associated with communicating hydrocephalus from other causes (14). They are the result of damage to midline basal structures by the infectious process which at the same time may obliterate the basal cisterns.

All of the progressing hydrocephalic patients showed increased cerebrospinal fluid pressure, but this was not necessarily reflected in the eye grounds. Optic atrophy was present in several and was secondary to the chiasmatic arachnoiditis constricting the optic nerves and thus preventing the appearance of papilledema. Significant papilledema was present in 7 cases and represents a warning sign. Emesis, confusion, and lethargy were more frequently present in cases of progressing hydrocephalus than in others. These signs and symptoms often associated with hydrocephalus (table 4) may be helpful in arousing suspicion of an advancing hydrocephalus, but air studies were necessary in all instances to establish firmly the true situation.

A striking finding observed in 2 cases is demonstrated in figure 11. In figure 11*A* and *B* are indicated a moderate communicating hydrocephalus with an

TABLE 4

SYMPTOMS AND SIGNS OF POSSIBLE SIGNIFICANCE IN PEDIATRIC CASES

Patient Number	Fundi	Emesis	Confusion, Lethargy, Coma	Brain Stem Deficits	Skull Resonance; "Cracked-Pot"	Suture Separation	Cerebrospinal Fluid Pressure mm/Hg	Cerebrospinal Fluid Protein mg. per 100 ml
Advanced hydrocephalus (7):								
24, M.C.	Normal	0	+	Nystagmus, ataxia	+	+	300 (v)	116
25, M.C.	Primary atrophy	+	+	Internuclear palsy	+	+	260 (v)	3,600
26, L.G.	Papilledema	+	+	Decerebrate tonic adversive seizures, rigidity	+	+	350	76
28, L.I.	Minimal atrophy	+	+	Sixth N. palsy	?	0	120	428
30, D.K.	Primary atrophy	+	+	Nystagmus, tonic adversion	+	+	100	112
38, A.R.	Primary atrophy	+	+	Decerebrate, paraplegia	+	+	200	100
45, R.L.	Papilledema	+	+	Dysconjugate gaze	+	0	Over 500	300
Moderate hydrocephalus (8):								
27, M.H.	Papilledema	+	0	Internuclear palsy	0	0	280	300
29, W.J.	Papilledema	+	+	Pupils unequal, tonic seizures	0	+	380	74
34, T.H.	Normal	+	+	Partial decerebration	+	+	120	310
36, W.O.	Normal	0	0	Unequal pupils	0	0	90	158
39, B.R.	Papilledema	+	+	Internuclear palsy, rigidity, tremor	0	+	580	244
43, J.O.	Normal	+	0	0	0	0	162	127
44, K.A.	Papilledema	+	+	Internuclear palsy, ataxia, rigidity	+	+	600	126
42, M.W.	Papilledema	+	0	Bilateral pyramidal signs, third N. palsy, partially decerebrated	0	+	240	540
Minimal hydrocephalus (2):								
32, W.M.	Minimal papilledema	+	0	Nystagmus	0	0	380	135
41, M.W.	Normal	0	0	Minimal strabismus	+	0	100	178
No hydrocephalus (8):								
21, J.A.	Minimal atrophy	+	0	0	+	0	100	62
22, J.B.	Normal	+	+	Sixth N. palsy	0	0	280	93
23, E.B.	Normal	+	0	0	+	0	140	152
31, L.L.	Normal	+	0	0	0	0	90	55
33, G.L.	Normal	+	+	Sixth N. palsy	0	0	40	5,440 (lumbar)
35, J.O.	Normal	+	0	0	0	0	162	127
37, D.L.	Normal	+	+	0	0	0	190	130
40, C.S.	Normal	0	0	0	0	0	170	110

enlarged fourth ventricle (dots) and obstruction in the basal cisterns (arrows). High intracranial pressure had caused suture separation. In figure 11*C* the floor of the third ventricle was invaginated (dots) and elevated by a mass just anterior to the obstructed upper cisterna pontis (arrows). This was presumed to be the tuberculous exudative reaction in the cisterna chiasmaticus and interpeduncularis. Ventriculo-mastiodostomy was necessary, but recovery was not as prompt as was expected. A serial pneumoencephalogram obtained six months later (figure 11*D*) showed little change in the basal cisternal mass, but normal intracranial pressure was present with closure of the skull suture lines. The obstructed cerebrospinal fluid pathways remained obstructed even under intensive antituberculous therapy as previously observed (5, 10, 12), and the chronic inflammatory mass did not resolve. The patient's clinical recovery was very good, however.

Five patients, 4 in the pediatric group and one young adult, showed excellent clinical response to their initial treatment but later developed a progressing hydrocephalus after the cerebrospinal fluid had been entirely negative for tubercle bacilli on culture for one or more years (table 5). Four of these patients had communicating hydrocephalus on the initial air study, and 3 of these had ventriculo-mastoid shunts performed. At the time of the delayed progression in 4 cases, there was no clinical evidence of change at the time the air study was done. The cerebrospinal fluid was entirely negative. A ventriculo-mastoid shunt was needed in 3 of these 4 patients, but only two of them accepted operation. Both made excellent recoveries. *Case 2* did not progress sufficiently to require reoperation.

TABLE 5

DELAYED PROGRESSION OR APPEARANCE OF HYDROCEPHALUS AFTER APPARENT BACTERIOLOGIC CURE

Patient Number	Age	Original Degree of Hydrocephalus	Original Operation	Onset of Meningitis to Delayed Change	Duration of Negative Cerebrospinal Fluid (Culture)	Result
2, J.M.	19 years	Moderate	Shunt	14 months	12 months	No operation; near normal
42, M.W.	6 months	Moderate	0	3 years	2 years, 11 months	Refused operation; died
32, W.M.	10 years	Minimal	Shunt	3½ years	3 years, 5 months	Reoperation; near normal
27, M.H.	4 years	None	0	14 months	12 months	Shunt; near normal
29, W.J.	3½ years	Moderate	Shunt	2 years	1 year, 10 months	Reoperation; minimally impaired

The one patient in this group for whom operation was refused (*Case 42*) died of his progressing internal hydrocephalus three and one-half years after onset of his meningitis. The cerebrospinal fluid had been negative on culture for tubercle bacilli on repeated examination for more than three years prior to death. In figure 12*A* and *B* the pneumoencephalogram done two years after onset of his meningitis is shown. The moderate communicating hydrocephalus was assumed to be arrested at that time since the patient had shown no neurologic changes for six months previously although his cerebrospinal fluid pressure was mildly elevated. He had been discharged from the hospital, but was recalled ten months later as a routine follow-up. He was found then to have deteriorated minimally, and the serial pneumoencephalogram showed definite advancement of his internal hydrocephalus (figure 12*C* and *D*). Operation was strongly advised but was refused by the parents. The child subsequently died six months later from steadily increasing intracranial pressure. The cerebrospinal fluid showed no recurrence of cells and remained negative to culture, but the post-mortem examination showed a number of active tubercles in the chronic granulomatous mass in the basal cisterns. Advanced communicating hydrocephalus was the cause of death.

The patient of *Case 27* (table 5) likewise showed delayed ventricular enlargement and had minimal hydrocephalus on the initial air study (figure 13*A*). Ventriculo-mastoidostomy was done and functioned well for six months with revision. Serial pneumoencephalography fourteen months after the initial study showed definite advance of ventricular enlargement (figure 13*B*) and reduced hemispheric subarachnoid air. The patient's clinical status and cerebrospinal fluid findings remained excellent, however, for an additional nine months. At that time headache, lethargy, and minimal brain-stem deficits appeared. A pneumoencephalogram two years after the first one (figure 13*C*) showed a block of the aqueduct of Sylvius (crosses) and a now complete block to oxygen in the basal cisterns (arrows). An immediate ventriculogram (figure 13*D*) showed advanced ventricular dilatation. A Torkildsen operation to by-pass the aqueduct block was done, but the results were not satisfactory. A subsequent ventriculo-mastoidostomy was life saving and the child now is nearly normal.

The delayed block in the aqueduct presumably was secondary to a subependymal tubercle or tuberculoma in the aqueduct (6), which developed late in the course of his disease, blocking the flow of cerebrospinal fluid and causing an obstructive hydrocephalus. At about the same time, the basal tuberculous arachnoiditis in the basal cisterns apparently progressed and caused a complete block to cerebrospinal fluid passage at that point as well. Two obstructions to cerebrospinal fluid flow occurred almost at the same time without evidence of recurrent activity in the cerebrospinal fluid findings, a rare occurrence (6). The Torkildsen procedure, by-passing the aqueduct obstruction with a tube from the lateral ventricles to the cisterna magna in the posterior fossa, was not effective, since it merely converted an obstructive hydrocephalus into a frank communicating hydrocephalus. When this was recognized, a ventriculo-mastoid shunt was done, resulting in steady improvement to nearly normal.

Presumably a reactivation or flare-up of tuberculous activity in the basal arachnoiditis in these 5 patients caused the delayed complications of hydrocephalus. The post-mortem findings in the one fatal case indicate this probability. It is also possible, however, that progressive cicatricial changes in the granulation tissue resulted in ultimate complete block of cerebrospinal fluid pathways without tuberculous activity (23, 28). Such progressive changes in cicatrix are well recognized. Intermittent or chronic activity of the tuberculous meningitis can cause intracranial calcifications (29), but none was observed here. The normal cerebrospinal fluid findings, except for pressure, were misleading, and serial pneumoencephalography was essential in establishing the true course of events.

SUMMARY

Pneumoencephalography used early in 45 patients with tuberculous meningitis revealed a startling difference in findings between the adults (20 patients) and the children (25 patients).

In the adult group, one patient showed progressing communicating hydrocephalus, and the findings in the other cases were probably consistent with the usual pneumoencephalographic findings in any similar age and socio-economic group. The pneumoencephalographic studies in the pediatric patients, however, showed a 68 per cent incidence of communicating hydrocephalus which was classified as advanced, moderate, or minimal. By serial pneumoencephalography, only 2 of the 17 cases of hydrocephalus showed spontaneous arrest. The remaining 15 were progressive and the patients required surgical treatment.

An hydrocephalic syndrome was not clearly recognizable in the clinical signs and symptoms of children who developed communicating hydrocephalus although variable brain-stem deficits and evidence of increased intracranial pressure were always present. Clinical prediction of early hydrocephalus was therefore difficult and inaccurate.

All of the 8 deaths occurred in the pediatric patients. All deaths occurred in children with advanced or moderate hydrocephalus, indicating again the seriousness of this complication.

The average time interval between onset of meningitis and start of therapy was sixteen days in the children with advanced and moderate hydrocephalus as well as in the children with no hydrocephalus. This interval was fourteen days in the adults. Treatment delay within the sixteen-day interval would seem to have little effect on the development of the hydrocephalus.

Five cases of delayed hydrocephalus were demonstrated by serial pneumoencephalography, which occurred from one to three and one-half years after the cerebrospinal fluid findings had become normal and had remained normal. Operative treatment of the increased pressure was indicated in 4 patients. Pneumoencephalography used early in tuberculous meningitis and serially thereafter produced no complications in activating the tuberculous process. The advantages of such early initial and serial use are:

(*a*) early diagnosis of the communicating hydrocephalus

(*b*) determination of the progressive nature of the hydrocephalus
(*c*) serial control on the effectiveness of hydrocephalus treatment
(*d*) prognostic value when hydrocephalus was absent
(*e*) recognition of delayed changes producing communicating or obstructive hydrocephalus one to three years after the onset of meningitis and associated with normal cerebrospinal fluid findings.

SUMARIO

La Neumoencefalografía en la Meningitis Tuberculosa

La neumoencefalografía usada tempranamente en 45 enfermos de meningitis tuberculosa reveló una diferencia sorprendente en los hallazgos entre los adultos (20 enfermos) y los niños (25 enfermos).

En el grupo adulto, un enfermo mostró hidrocefalia comunicante progresiva y en los demás casos los hallazgos neumoencefalográficos se conformaban probablemente a lo habitual a cualquiera edad y grupo socioeconómico semejantes. Sin embargo, en el grupo pediátrico, los estudios neumoencefalográficos revelaron una incidencia de 68 por ciento de hidrocefalia comunicante que se clasificó como avanzada, moderada o mínima. Con la neumoencefalografía seriada, sólo 2 de los 17 casos de hidrocefalia mostraron estacionamiento espontáneo. Los 15 restantes fueron evolutivos y los enfermos requirieron tratamiento quirúrgico.

Aunque siempre había déficits variables en el bulbo raquídeo y signos de hipertensión intracraneal, no cabía reconocer netamente el síndrome hidrocefálico por los signos clínicos y síntomas en los niños que manifestaron hidrocefalia comunicante, siendo por ello difícil e inexacta la predicción clínica de hidrocefalia incipiente.

Todas las 8 muertes ocurrieron en los enfermos pediátricos. Todas recayeron en niños que tenían hidrocefalia avanzada o moderada, indicando así de nuevo la gravedad de esta complicación.

El tiempo transcurrido entre la aparición de la meningitis y la iniciación de la terapéutica promedió dieciséis días en los niños que tenían hidrocefalia avanzada o moderada así como en los que no tenían hidrocefalia. El promedio fué de catorce días en los adultos. La tardanza terapéutica dentro del plazo de dieciséis días pareció ejercer poco efecto sobre la aparición de la hidrocefalia.

Cinco casos de hidrocefalia tardía fueron revelados por la neumoencefalografía en serie, lo cual sucedió de uno a tres años y medio después de normalizarse los hallazgos del líquido céfalorraquídeo y permanecer normalizados. En 4 enfermos se hallaba indicado el tratamiento operatorio de la hipertensión. La neumoencefalografía usada tempranamente en la meningitis tuberculosa y en serie a partir de entonces no produjo complicaciones en lo tocante a activar el proceso tuberculoso. Las ventajas de ese empleo temprano y seriado son:

(*a*) diagnóstico temprano de la hidrocefalia comunicante
(*b*) determinación de la naturaleza evolutiva de la hidrocefalia
(*c*) cotejo seriado de la eficacia del tratamiento de la hidrocefalia
(*d*) valor pronóstico cuando no hay hidrocefalia
(*e*) reconocimiento de las alteraciones tardías que producen hidrocefalia comunicante u oclusiva de uno a tres años después de la iniciación de la meningitis y unidas con hallazgos normales en el líquido céfalorraquídeo.

RESUME

Pneumoencéphalographie dans la méningite tuberculeuse

La pneumoencéphalographie utilisée précocement chez 45 malades atteints de méningite tuberculeuse a révélé une différence saisissante entre les résultats obtenus chez l'adulte (20 malades) et chez l'enfant (25 malades).

Dans le groupe adulte, un malade présentait une hydrocéphalie communiquante progres-

sive et les clichés obtenus dans les autres cas paraissaient comparables à ceux obtenus dans un groupe d'âge et de conditions socio-économiques analogues. En pédiatrie, les recherches pneumoencéphalographiques ont toutefois montré une incidence de 68%, pour l'hydrocéphalie communiquante, qui fut classifiée comme avancée, modérée ou minime, la pneumoencéphalographie en série n'a révélé que 2 cas d'hydrocéphalie sur 17 qui aient présenté un arrêt spontané. Les 15 autres étaient progressifs et les malades étaient justiciables du traitement chirurgical.

Chez les enfants, le syndrome hydrocéphalie n'était pas nettement identifiable par ses signes cliniques et ses symptômes lorsque celui-ci se développait, bien que diverses altérations du tronc cérébral et l'hypertension cranienne fussent toujours présentes. Un pronostic clinique de l'hydrocéphalie au début était donc difficile et imprécis.

La totalité des huit décès s'est produite chez les enfants. Tous les décès sont survenus chez des enfants présentant une hydrocéphalie de degré avancé ou modéré, ce qui indique encore la gravité de cette complication.

La durée moyenne de l'intervalle entre le début de la méningite et l'institution du traitement était de seize jours chez les enfants atteints d'hydrocéphalie avancée ou modérée de même que chez ceux sans hydrocéphalie. Cet intervalle était de quatorze jours chez l'adulte. Le délai du traitement avec intervalle de seize jours ne paraît avoir eu que peu d'influence sur le développement de l'hydrocéphalie.

Cinq cas d'hydrocéphalie tardive furent démontrés par la pneumoencéphalographie en série, qui fut effectuée de un à trois ans et demi après que l'examen du liquide céphalo-rachidien soit redevenu et resté normal. La décompression chirurgicale d'une hypertension croissante fut indiquée chez 4 malades. Dans la méningite tuberculeuse, la pneumoencéphalographie utilisée précocement et ensuite en série, n'a entraîné aucune complication par activation du processus tuberculeux. Les avantages de cet emploi précoce, puis en série sont:

(*a*) diagnostic précoce de l'hydrocéphalie communiquante,
(*b*) détermination de la nature évolutive de l'hydrocéphalie,
(*c*) contrôle en série de l'efficacité du traitement, de l'hydrocéphalie,
(*d*) valeur pronostique en l'absence d'hydrocéphalie,
(*e*) démonstration des altérations tardives produisant l'hydrocéphalie communiquante ou obstructive de un à trois ans après le début de la méningite alors que le liquide céphalo-rachidien est normal.

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THE SURGICAL TREATMENT OF EMPHYSEMATOUS BULLAE[1,2]

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INTRODUCTION

The treatment of emphysematous bullae, either medical or surgical, has been so completely discouraging as to prompt a widespread attitude of hopelessness.

Purely medical treatment is ordinarily directed toward the problems of keeping the airway open, prevention or correction of complicating infection, and reduction of physical activity to compensate for the loss of pulmonary efficiency. This reduction of activity eventually reaches the point of total disability. It is obvious, therefore, that medical treatment is purely palliative and is effective for only a limited period of time. Surgical treatment directed toward the extirpation of bullae-containing units is rational treatment only in that very small number of patients whose emphysematous bullous disease is limited to the pulmonary unit which can be removed. Therefore, if a surgical program of treatment is to be successfully applied to the larger and more seriously ill group of patients who are increasing in number, a procedure other than pulmonary resection must be developed.

The progressive dyspnea in bullous emphysema is not due primarily to reduction in the capability of function of pulmonary units, but rather to the progressive compression of pulmonary parenchyma by enlarging cysts. An attempt has been made, therefore, to apply a surgical program of treatment directed toward the release and return to proper function of the lung units so entrapped and compressed. The approach chosen represents a departure from the sporadic attempts which have been made to apply pulmonary resection, or the even more irrational Monaldi drainage and suction procedure, to these cases.

Procedure

The method of surgical treatment employed is directed toward the obliteration of the bullae and consists of the excision of the pleural roof and approximation of the parenchyma, which forms the walls, and the pleura with a continuous suture of fine chromic catgut, each bite including a minimal depth of parenchyma. It is unnecessary to attempt the individual ligation of the many air leaks unless a relatively large bronchial communication is encountered, since the obliteration of the bullae will accomplish this purpose. The bullae lack a mucous membrane, and healing by first intention occurs.

RESULTS

The writers have treated 18 cases of emphysematous bullae at thoracotomy. The problem of the selection of these thoracotomy cases for major surgery has not

[1] From the Ingham Chest Hospital, Lansing, Michigan.

[2] Presented, in part, before the Medical Session, as part of *Section 2A*, at the annual meeting of the National Tuberculosis Association, Milwaukee, Wisconsin, May 23, 1955.

been great. All of the patients had obvious respiratory insufficiency, due to either compression of the lung or to pneumothorax, which did not respond to conservative measures. The results have been gratifying. Pulmonary function tests made from six months to four years after surgery reveal an excellent pulmonary reserve, considering the extent of emphysema present. The fact that these men have returned to work, some as laborers, speaks for itself.

There has been no mortality. In one case of spontaneous pneumothorax due to rupture of an emphysematous bulla, failure to maintain complete expansion after thoracotomy necessitated a thoracoplasty. The clinical result obtained in this case was considered to be good. Two cases (*Cases 3* and *4*) required intercostal suction for two weeks postoperatively.

It would appear that the failure to obtain improvement in pulmonary function as reported by others is due to the fact that pulmonary units containing bullae are resected instead of being preserved and returned to a functioning state with the bullae obliteration procedure. In the writers' own experience with pulmonary resections, significant degrees of clinical improvement were likewise not obtained, and there were many patients who were not considered to be suitable risks for the resection of pulmonary segments or lobes. The writers are unable to understand the conflicting statements of those surgeons who say they have no difficulty with pulmonary resection in bullous emphysema and at the same time report failure to attain clinical improvement.

The improvement in the cardiorespiratory reserve at the time of surgery, the absence of mortality, the low morbidity, and the clinical results justify the contention that thoracotomy and obliteration of bullae by this method should not be denied these respiratory cripples.

As a matter of fact, increasing attacks and severity of respiratory infection, the observation of increasing size of bullae on serial chest films, diminishing pulmonary reserve clinically and as measured by periodic pulmonary function tests should be considered indications for surgical treatment before a state of invalidism is reached.

Differentiation of Congenital Cystic Disease from Emphysematous Bullae

As this method of management of emphysematous bullae cannot be successfully applied to lesions of congenital cystic disease (1, 2), differentiation of the latter is therefore important. Congenital cystic bronchiectasis obviously demands the resection of the entire lung units involved (*Cases 1* and *4*). The mucous membrane of isolated congenital cysts is not conducive to healing even with apposition of the walls (1).

The continued ability to form secretions favors recurrence and infection with or without ligation of bronchial communications. In some cases the cyst is separated from the normal parenchyma by a layer of pleura and can be enucleated (*Case 3*). Another type of congenital cyst is that with the mucous membrane of the base intimately and directly attached to the parenchyma. Enucleation of these cysts is to be condemned (1). This type can be treated by the excision of the roof, consisting of mucous membrane and pleura, and the ligation of the bronchial communications, allowing the base to evert and become adherent to

the parietal pleura with the application of positive pressure and the maintenance of expansion during the postoperative period (*Case 2*). If this method does not seem feasible, an alternative procedure for the treatment of these subpleural cysts and also the more deeply lying congenital cysts is lobectomy (3), since the dissection of the wall from the underlying parenchyma entails difficult hemostasis and control of air leaks. Furthermore, the necessity for the preservation of parenchyma is not as vital as it is in the treatment of emphysematous bullous disease with underlying widespread emphysema.

The differentiation between emphysematous bullous disease and congenital cystic disease is not only important from the standpoint of the selection of the proper procedure at the time of thoracotomy, but also because consideration of thoracotomy is reserved for those cases of emphysematous bullous disease in which respiratory insufficiency is present or imminent. The extirpation of congenital cysts, however, is also indicated for the eradication of a source of infection, hemorrhage, and malignant degeneration (4) and in those cases in which the exclusion of other pulmonary disease, including malignancy, cannot be certain.

The history of those presenting with emphysematous bullous disease is related to the fundamental cause and is characterized by attacks of bronchitis and asthma which occur over a period of years. In some patients, symptoms do not precede the onset of respiratory insufficiency or spontaneous pneumothorax. These cases probably represent emphysema with bullae formation resulting not from bronchial disease but degeneration of elastic tissue. The typical changes of emphysema are found on physical examination and chest roentgenograms, in which the bullae are recognized by the absence of lung markings and definite walls, with fine discrete filaments traversing the space at angles to the usual lung markings. These bullae are usually bilateral and often present in all lobes. However, fluid formation and infection do not occur in these spaces, due to the absence of a secreting mucous membrane and the filtration of air before entrance to the spaces through the bronchiolar communications (4). Congenital cysts, on the other hand, when air is present within them, usually have a discrete outline with definite walls, and are usually limited to a lobe or at least a definite lung area. These cysts are often discovered on routine chest roentgenography, although often they may present a clinical history and picture of an acute infection, in which case a fluid level is often seen in the cyst (4).

Spontaneous or traumatic pneumothorax (*Cases 5* and *6*) is a frequent complication of emphysema with bullae and bleb formation (5, 6). Forty-three of the writers' patients, ultimately requiring thoracotomy, presented with spontaneous pneumothorax. The thin, pleural roof (figure 15) without a mucous membrane lining and the absence of adhesions and collateral circulation are probably the important factors contributing to this complication. There would appear to be no correlation between the degree of physical activity and the onset of pneumothorax. Seventy per cent of the writers' cases of spontaneous pneumothorax occurred at rest in bed or even during sleep. This would indicate that the air leak occurs at a point of necrosis of the pleural roof.

Pneumothorax is rarely, if ever, a complication of congenital cystic disease.

The thickness of the walls which have a definite lining (figure 12) and the frequency with which pleural adhesions are observed in these cases at thoracotomy support the opinion expressed above regarding the etiology of spontaneous pneumothorax.

It is interesting that thus far the writers have observed in females no case of emphysema with bullae formation of sufficient severity to indicate consideration for thoracotomy. On the other hand, congenital cystic disease does not occur more frequently in either sex.

Bronchography is often helpful in determining the extent of involvement in congenital cystic disease (*Cases 1, 2,* and *4*), especially in cases of bronchiectasis.

The viscosity of the contrast medium prevents its entrance into the emphysematous bullae through the bronchiolar communications (*Cases 7* and *8*); however, bronchography in these cases does serve to indicate the degree of bronchial distortion and the size of the spaces (7).

The inability to arrive at a definite etiologic diagnosis in any given case of respiratory insufficiency due to either congenital or acquired cystic disease should not serve as a deterrent to thoracotomy. The diagnosis made at exploration should indicate the procedure of choice. The absence of inflammatory changes, the thin flaccid pleural roofs (figure 14), the multiplicity of the lesions, the involvement of multiple lobes, the absence of a mucous membrane with a base made up of denuded lung tissue with attenuated strands traversing the spaces, and the many small air leaks establish the diagnosis of emphysematous bullae (8).

DISCUSSION

Emphysema due to the loss of support of alveolar walls and intermittent partial bronchial obstruction results in various physiologic and pathologic pulmonary changes; some of these are self limited. As an illustration, compensatory emphysema of a normal lobe resulting from atelectasis of another lobe is produced by an increase in the negativity of the intrapleural pressure and a relative decrease in the support of the alveolar wall. Normal intrapleural pressures are regained by the compensatory emphysema, and the process is arrested. Pneumonia in children is known to be followed by the development of bullae which result from necrosis of alveolar and bronchiolar walls and the increase of intrabronchial pressures, due to a mechanical obstruction of mucous plugs and the tendency of relatively flexible bronchial walls to approximate during expiration and especially during coughing, sneezing, and straining. The fact that the emphysema spontaneously regresses after infection has subsided is an indication of the ability of the uninvolved parenchyma to obliterate the spaces by virtue of its inherent elasticity (9). The paradoxical obstructive emphysema of a lobe due to a foreign body, a congenital web, or mucosal folds may progress to the point of complete atelectasis of the remaining lobes and can be corrected by the removal of the foreign body (10) or extirpation of the emphysematous lobe (11).

* * *

In contrast to the preceding types, the emphysema resulting from factors which are practically inherent, that is, the degeneration of elastic tissue and

bronchiolar spasm, is progressive. At best, conservative measures directed toward diminishing the volume of the thoracic cage and relieving bronchiolar obstruction due to spasm and mucus can only diminish the rate of progression of this insidious disease. The distention of alveoli leads to the breakdown of the inter-alveoli septa, and bullae are produced. With the formation of emphysematous bullae, new factors result and hasten the progression towards respiratory insufficiency. Neighboring alveoli, still capable of function, are compressed by the bullae and are rendered atelectatic and subject to infection. The pulmonary structure offers little resistance to the expansion of emphysematous bullae. Any increase in pressure within the cavity over that in the bronchial communications immediately forces the attenuated parenchyma over them, thus frustrating any tendency to empty the bullae of air. Indeed, as a result of thoracoscopic study of these bullae, it is believed that, once bullae have been formed, air enters these structures during expiration. During inspiration the bronchial communications are compressed by the positive pressure within the bullae while a relatively negative pressure is present within the bronchial tree (12, 13). Coughing and straining, which are prevalent, especially during complicating respiratory infection, result in tremendous increases of intrabronchial pressure to distend bullae (12). Thus, the vicious cycle of respiratory infection and enlarging bullae is superimposed upon the basic disease process (figure 11).

* * *

After consideration of these factors, it is reasonable that the evacuation of bullae with the preservation of parenchyma, functional or potentially capable of function, to allow expansion of the lung to fill the hemithorax with minimal contribution to emphysema should be the aim of treatment (2, 12, 14). Resection, advocated in the past, is to condemned (8, 15, 16, 17). The extirpation of lung units containing bullae not only sacrifices functioning alveolae and those capable of function within that unit (figure 13), but also contributes to the forces of the basic disease process and results in further overdistention of the remaining alveolae. It has been pointed out that one tends to overestimate the extent of permanent pulmonary damage, not only in evaluation of chest roentgenograms but at thoracotomy, that a cyst or cysts thought to occupy an entire lobe (or even an entire hemithorax) may, upon unroofing and allowing the atelectatic lung to expand, be limited to a lobe or even a segment (12). Furthermore, although emphysematous bullae are in the great majority of cases multiple and at thoracotomy the prospects of treating the many bullae individually are discouraging, it may be found upon unroofing a bullae that there are communications with other bullae, all of which may be treated as a single space.

The institution of Monaldi drainage in the treatment of emphysematous bullae is said to have been highly successful in other hands (13). However, there are many objections to this method (8). Many cases of advanced emphysematous bullous disease present with spontaneous pneumothorax, and obviously cannot be treated by Monaldi drainage. As a matter of fact, in the experience of the writers, the high percentage of failure to expand lungs collapsed by the spontaneous or traumatic rupture of emphysematous bullae by the institution of

closed intercostal drainage have indicated the futility of using Monaldi drainage. Other objections are: the lack of adaptability to the treatment of multiple bullae; the necessity of a preliminary procedure to obtain pleural symphysis; the necessity of thoracoscopy, with its dangers and limitations, for accurate diagnosis; the determination of suitability for treatment; and the prolonged period of treatment and hospital care.

It would appear that the only justification for the blind percutaneous introduction of instruments into pulmonary cysts and bullae for purposes of examination, aspiration, and introduction of cauterizing agents is the fear of thoracotomy. Undoubtedly, thoracotomy in the past presented many dangers which are obviated with present methods. Respiratory insufficiency due to compression by cysts and bullae does not constitute a contraindication to thoracotomy. Indeed, the most desperately ill patient in the present series (*Case 10*), whose maximal breathing capacity was necessary to maintain life in bed, improved with the introduction of the endotracheal tube and the consequent decreased resistance to the flow of gases through the upper respiratory passages and reduction in dead air space. The aspiration of secretions and the application of positive pressure permits rapid expansion of functioning lung after the bullae have been unroofed. The greatly improved ventilation and diminished resistance of the pulmonary capillary bed result in continued improvement of these patients during the procedure, diminishing and even obviating the relative risk.

SUMMARY

Emphysematous bullous disease is progressive. With the formation of bullae, new factors, that is, paradoxical inflation and infection, are superimposed upon the basic disease process, establishing a vicious cycle and hastening the progress toward cardiorespiratory insufficiency.

Obliteration of the bullae at thoracotomy is the procedure of choice. Pulmonary resection of emphysematous bullae is to be condemned because it sacrifices lung potentially capable of functioning and contributes to overexpansion of the remaining lung and parenchyma. Percutaneous instrumentation is dangerous and unnecessary.

The rupture of emphysematous bullae, as well as bronchial tears, should be considered in the differential diagnosis of traumatic pneumothorax which fails to respond to conservative treatment. The principles of treatment of emphysematous bullae should not and/or need not be applied to congenital cystic disease.

SUMARIO

El Tratamiento Quirúrgico de las Flictenas Enfisematosas

El enfisema vesicular es evolutivo. Al formarse bullas, se sobreponen al proceso morboso fundamental nuevos factores, es decir, inflación e infección paradójicas, estableciendo un círculo vicioso y acelerando la evolución hacia la insuficiencia cardiorrespiratoria.

La obliteración de las vesículas en la toracotomía es el procedimiento de elección. Hay que condenar la resección pulmonar de las bullas enfisematosas por crear un sacrificio y contribuir a la excesiva expansión del pulmón y parénquima restantes. La instrumentación percutánea resulta peligrosa e innecesaria.

En el diagnóstico diferencial del neumotórax traumático que no responde al tratamiento conservador, deben considerarse la rotura de vesículas enfisematosas, así como los desgarros bronquiales. Los principios del tratamiento de las flictenas enfisematosas no deben y/o no necesitan aplicarse a la enfermedad quística congénita.

RESUME

L'emphysème bulleux est une affection progressive. Avec la formation de bulles, de nouveaux facteurs (inflation paradoxale et infection) se superposent au processus pathologique primitif, établissant ainsi un cercle vicieux et accélérant l'évolution vers l'insuffisance cardio-respiratoire.

L'oblitération des bulles par la thoracotomie est le procédé de choix. La résection pulmonaire des bulles est à condamner parce qu'elle entraîne le sacrifice de tissus et contribue à la surexpansion du poumon et du parenchyme pulmonaire restant. L'intervention percutanée est dangereuse et inutile.

La rupture des bulles d'emphysème, ainsi que les déchirures bronchiques, doivent être considérées dans le diagnostic différentiel du pneumothorax traumatique qui ne répond pas au traitement conservateur. Les principes du traitement des bulles d'emphysème ne doivent pas être appliqués ou n'ont pas besoin d'être appliquées á la maladie kystique congénitale du poumon.

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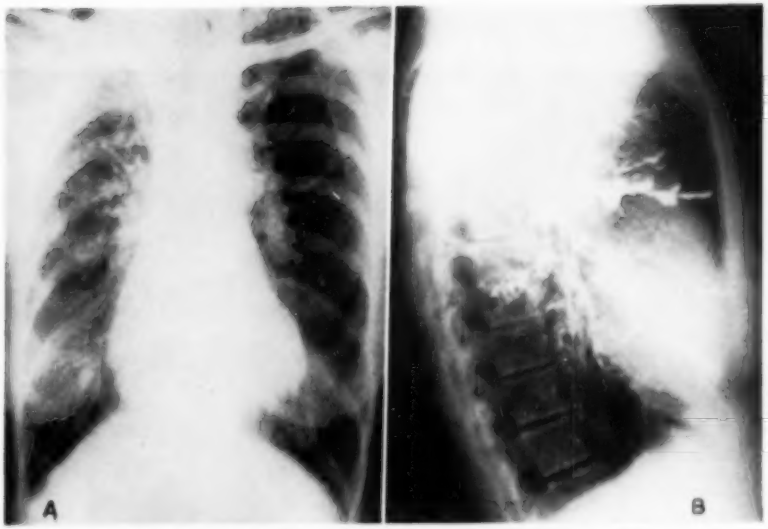

FIG. 1. *Case 1. A*. Standard film of a 62-year-old woman showing a wedge-shaped density and disruption of the bronchovascular markings in the right upper lobe. There was a history of frequent episodes of productive cough and fever for many years, two episodes of septic arthritis, and auricular fibrillation. *B*. Bronchogram revealing cystic bronchiectasis of the right upper lobe. The right upper lobe was removed, relieving the patient of symptoms and a possible source of bacteremia.

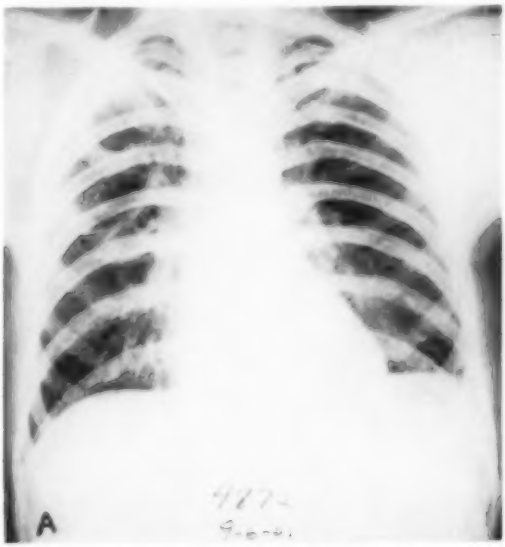

FIG. 2. *Case 2. A*. Standard film of a 26-year-old male with a cavity in the right upper lobe.

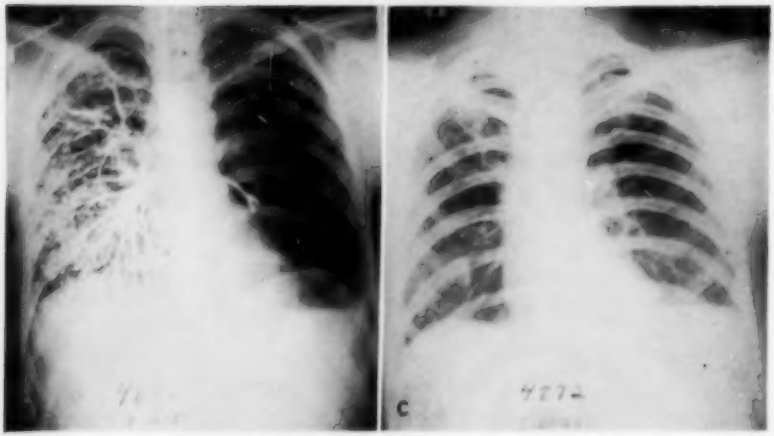

FIG. 2. *Case 2. B.* Bronchographic film with a fluid level in the cystic cavity. Pulmonary secretions were negative for tubercle bacilli. The patient was tuberculin negative. *C.* The result of excising the roof, consisting of pleura and cyst wall, of a single subpleural cyst and ligation of the bronchial communications to allow eversion of the mucous membrane base with inflation of the lung.

FIG. 3. *Case 3. A.* Standard film of a 62-year-old laborer, showing a large cyst in the left upper lobe, which the patient refused to have treated.

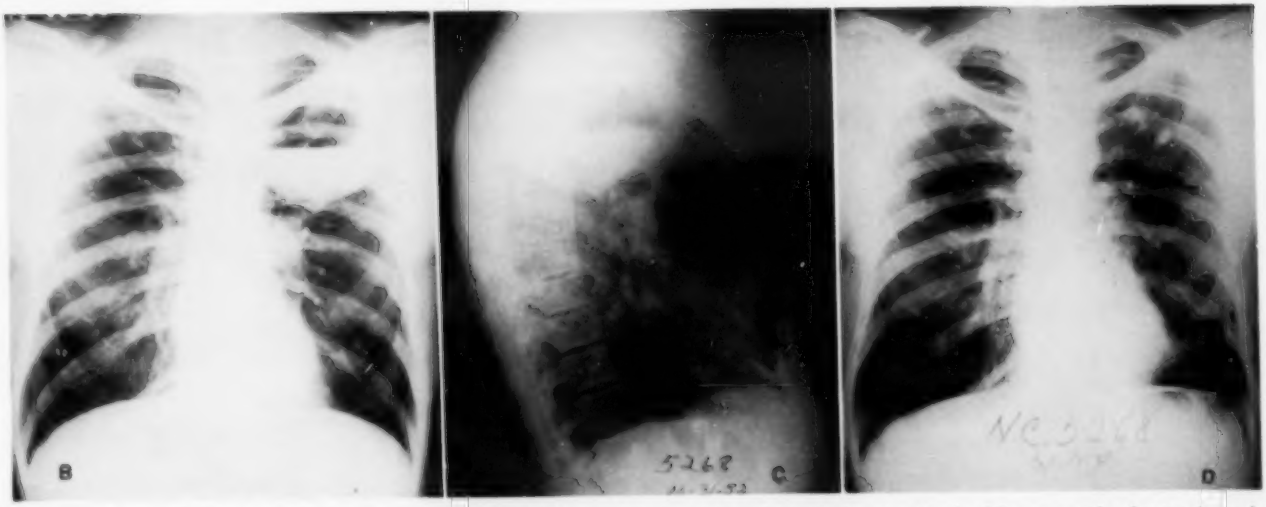

FIG. 3. *Case 3. B* and *C*. Anterior-posterior and lateral films taken seven years later during an attack of fever, cough, chest pain, and dyspnea. Note the fluid level. The cyst contained pus. *D*. The result after enucleation of the cyst and ligation of one bronchial communication. The cyst was invested with a complete pleural layer.

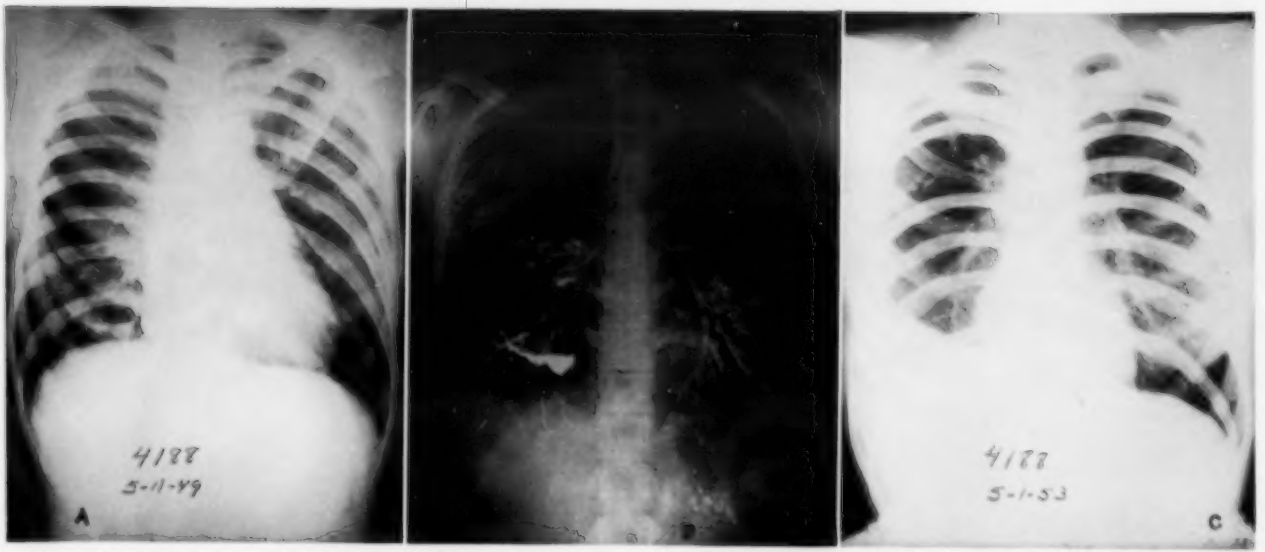

FIG. 4. *Case 4. A.* Standard film of a 21-year-old female with a productive cough, fatigue, and weight loss, showing an area of rarefaction in the right lower lung field. *B.* Bronchographic film. Three or four cystic dilations are noted in the right lower lobe. *C.* Following right lower lobe resection. The specimen revealed severe deep lying cysts with a definite smooth glistening lining and no obvious bronchial communications.

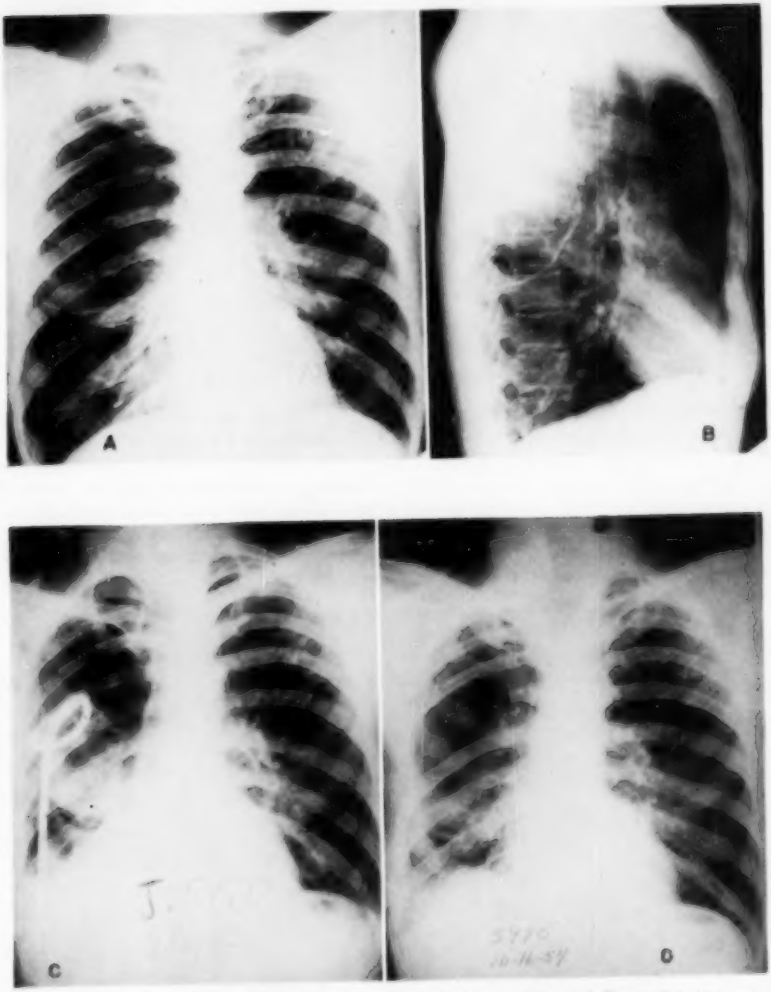

FIG. 5. *Case 6. A* and *B*. Standard anterior-posterior and lateral films of a 43-year-old male, showing large emphysematous bullae of the right lung and infiltration in the left upper lobe, which was being studied to determine its etiology. *C*. Spontaneous pneumothorax occurred during sleep while the patient was in the hospital for observation of the lesion in the left upper lobe. The right lung failed to re-expand after six days of closed intercostal drainage with suction. *D*. The result after unroofing and obliteration of the bullae at thoracotomy.

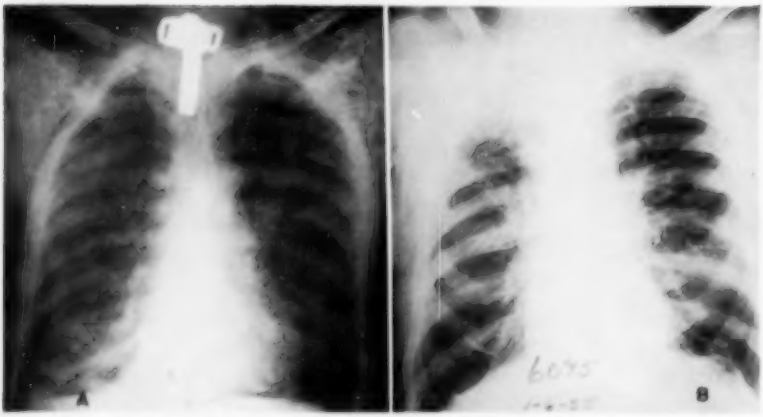

FIG. 6. *Case 6*. *A*. Standard film showing right pneumothorax, extensive rib fractures, and extensive subcutaneous emphysema with tracheotomy tube and closed intercostal drainage tube in place. The patient, a 65-year-old man, had been struck by a train. Aspiration of large amounts of air continued and subcutaneous emphysema extended to involve the entire body. Thoracotomy was elected in view of the strong possibility of a ruptured bronchus; a large emphysematous bulla, punctured by a spicule of rib bone, was found. *B*. Film shows the result of unroofing and obliteration of the bullous space. The thoracotomy tube was removed on the third postoperative day.

FIG. 7. *Case 7*. *A*. Standard film of a 60-year-old carpenter who had had progressive dyspnea for four years and was unable to work. Note the large bulla occupying at least 40 per cent of the right hemithorax. Also note the infiltrations off the left hilum.

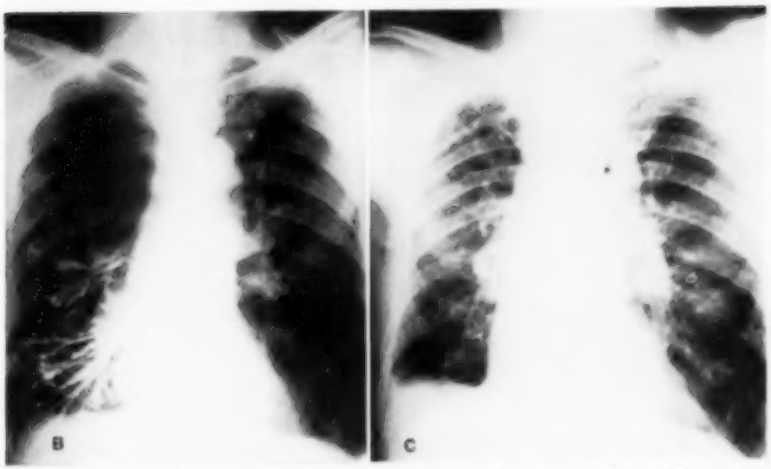

FIG. 7. *Case 7. B.* Bronchographic film confirming the size of the bulla. *C.* The result of unroofing and obliteration of a large bullous space at thoracotomy. The thoracotomy tube was removed on the sixteenth postoperative day, and he returned to work two months later. Pulmonary function walking ventilation, 22 liters per minute; maximal breathing effort, 39.5 liters per minute; ratio, 56 per cent.

FIG. 8. *Case 8. A.* Standard film of a 59-year-old laborer who had progressive dyspnea so that he was unable to walk more than 50 yards. Note the large bullae occupying the upper half of both lung fields.

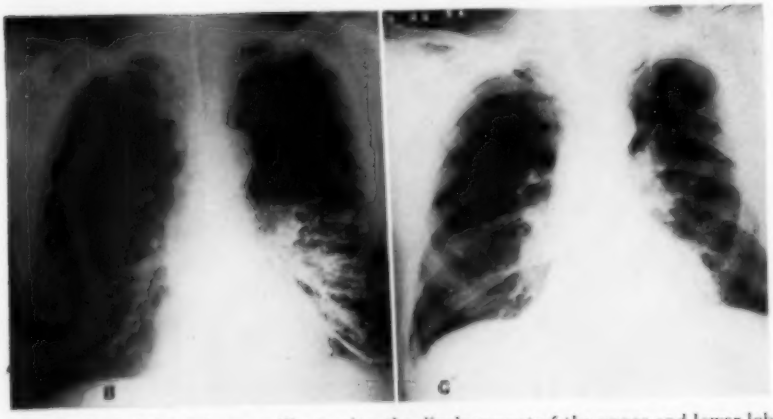

FIG. 8. *B*. Left bronchogram illustrating the displacement of the upper and lower lobes into the lower third of the chest. *C*. The result following unroofing and obliteration of the bullous spaces on the left. The patient returned to work six weeks after surgery. Pulmonary function: walking ventilation, 16 liters per minute; maximal breathing effort, 35 liters per minute; ratio, 46 per cent.

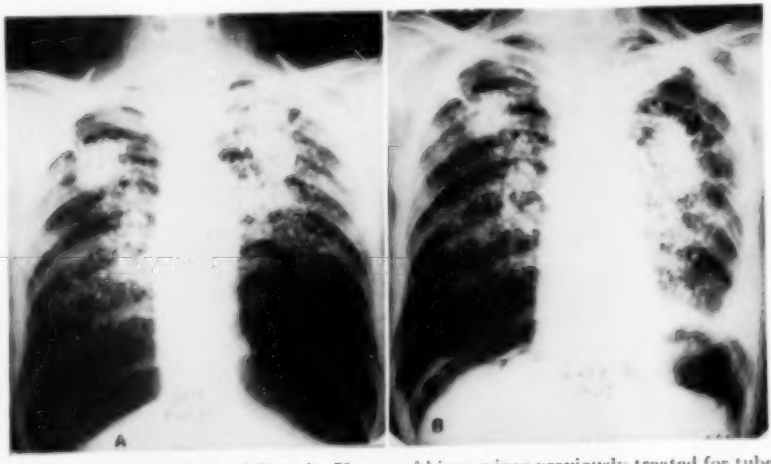

FIG. 9. *Case 9*. *A*. Standard film of a 53-year-old iron miner previously treated for tuberculosis. He complained of dyspnea for six years, progressing to complete disability. Note the large bullae occupying approximately 50 per cent of both lower lung fields and markedly depressing the diaphragm. *B*. The postoperative film. A tremendous bullous space was obliterated and 1,500 cc. of air were instilled into the peritoneal cavity to facilitate maintenance of expansion. A postoperative tracheotomy was performed because the patient could not initiate respirations without an artificial airway.

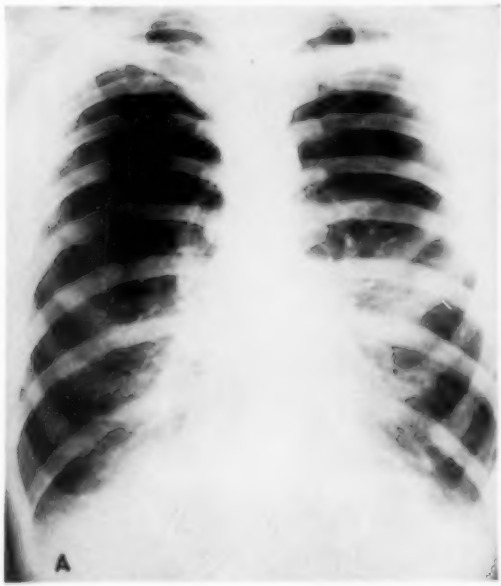

FIG. 10. *Case 10. A.* Standard film demonstrating large bullous spaces in both upper lung fields. At this time the patient was practically an invalid but refused operative intervention.

FIG. 10. *Case 10. B.* Thirty months later. Note the progression of the disease. At this time the patient was cyanotic on complete bed rest. The right lung is almost completely atelectatic from compression by the large bullae.

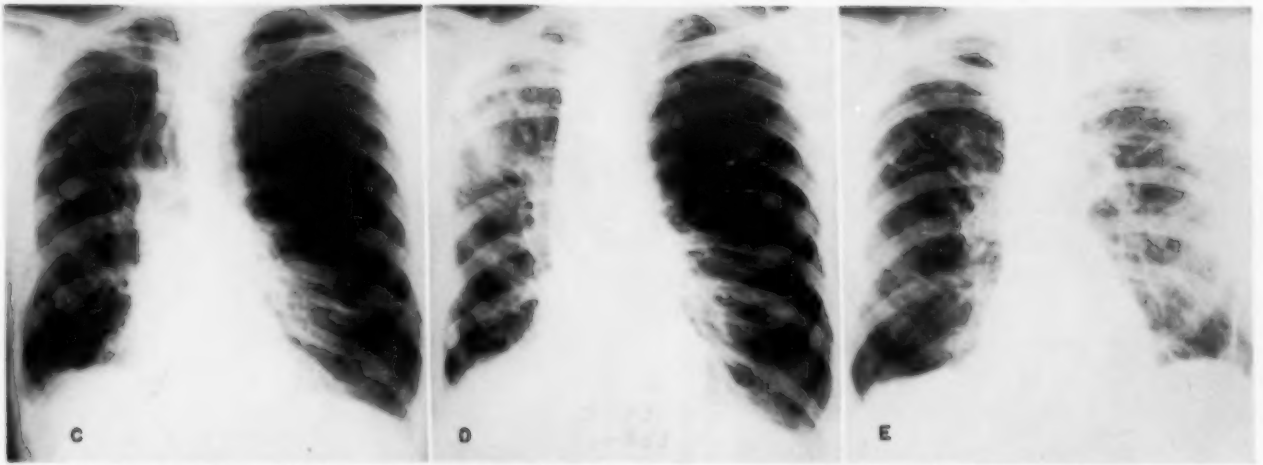

FIG. 10. *Case 10. C.* The result of unroofing and obliteration of large bullous spaces on the right. The patient was able to drive a truck three hours a day. *D.* Film demonstrates anterior mediastinal herniation of the left bullous spaces. Therefore, left thoracotomy was recommended and performed seven months after the first procedure. *E.* The final result. The patient had gained 50 pounds, was able to walk six blocks and climb two flights of stairs without dyspnea. He works eight hours a day. Pulmonary function: walking ventilation, 16 liters per minute; maximal breathing effort, 49 liters per minute; ratio, 34 per cent.

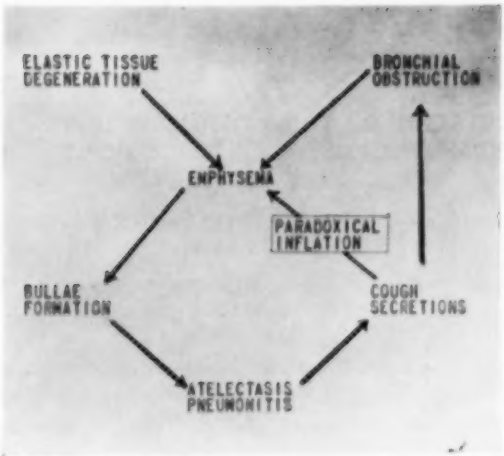

FIG. 11. Diagram illustrating the progressive character of bullous emphysema.

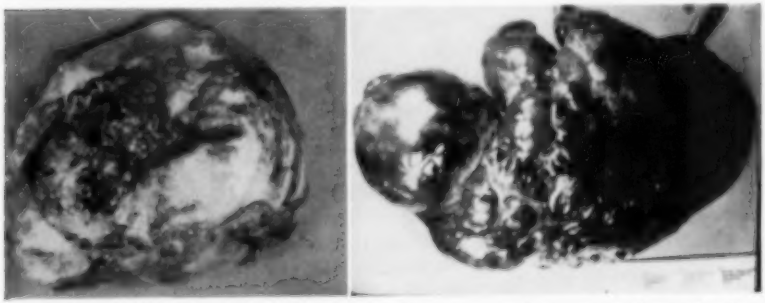

FIG. 12. (Left) Illustration of the thick leathery wall of the congenital cyst in *Case 3*.

FIG. 13. (Right) The resected lobe illustrating the compression of pulmonary parenchyma by a large bullous cyst. We no longer perform this operation for bullous emphysema.

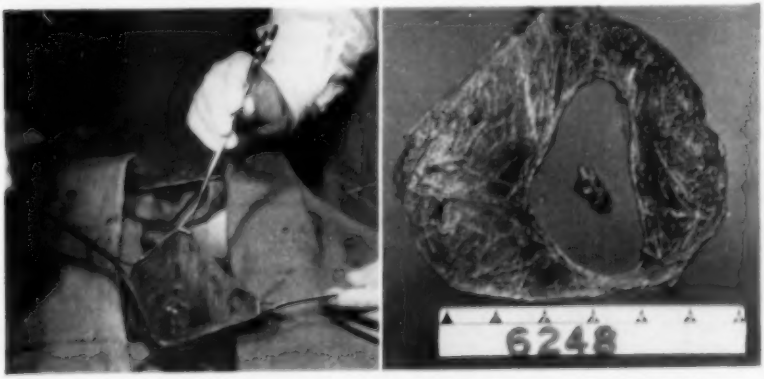

FIG. 14. (Left) A large bullous cyst opened at surgery in preparation for repair.

FIG. 15. (Right) The roof of the cyst illustrated in figure 14. Note the very thin wall of the cyst.

THE CORRELATION OF THE PATHOLOGY IN THE RESECTED BRONCHUS WITH POSTOPERATIVE COMPLICATIONS IN PULMONARY TUBERCULOSIS[1,2]

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INTRODUCTION

Resection of the lung in the treatment of pulmonary tuberculosis has become an accepted procedure during the past decade as the mortality rate and the number of complications associated with this technique have decreased. However, there remains a significant postoperative morbidity associated with bronchopleural fistula and empyema.

That parenchymal tuberculosis is often accompanied by involvement of the tracheobronchial tree has long been recognized (1–6). Chemotherapy has been shown to have a remarkable clearing effect upon this type of lesion (7). Recently, Medlar (8) again called attention to the microscopic findings in the bronchi draining an area of parenchymal disease and described the involvement of these bronchi as being either submucosal tubercle formation or lymphocytic infiltration along the bronchial wall.

The present study was undertaken to evaluate the relationship of the microscopic lesions of the bronchi to postoperative complications. The bronchi of 100 specimens resected between August, 1951, and June, 1955, were restudied.

METHOD OF INVESTIGATION

Originally an attempt was made to examine consecutive specimens, but it soon became apparent that an adequate and intact portion of the bronchus at the site of transection was not available in all cases and that such a study could not be accomplished. Specimens selected had been removed by segmental resection, lobectomy, pneumonectomy, or a combination of lobectomy and segmental resection. One centimeter of the bronchus at its proximal end was prepared histologically and multiple-step sections were taken. These were classified microscopically as being normal, showing submucosal lymphocytic infiltration, or showing tubercles. Microscopic examination of the 100 specimens demonstrated normal bronchi in 16 (figure 1), lymphocytic infiltration in 66 (figure 2), and tubercles in 18 (figure 3).

Clinical evaluation of the patients included sex, age, classification of disease, the presence or absence of tubercle bacilli in the sputum, the length of chemotherapy, the susceptibility or resistance of the tubercle bacilli, and bronchoscopic findings. The original pathologic findings were reviewed to determine whether open cavity or closed disease was present at the time of resection.

The complications investigated were residual space, bronchopleural fistula, and empyema. Any uninfected space remaining after segmental resection or lobectomy which

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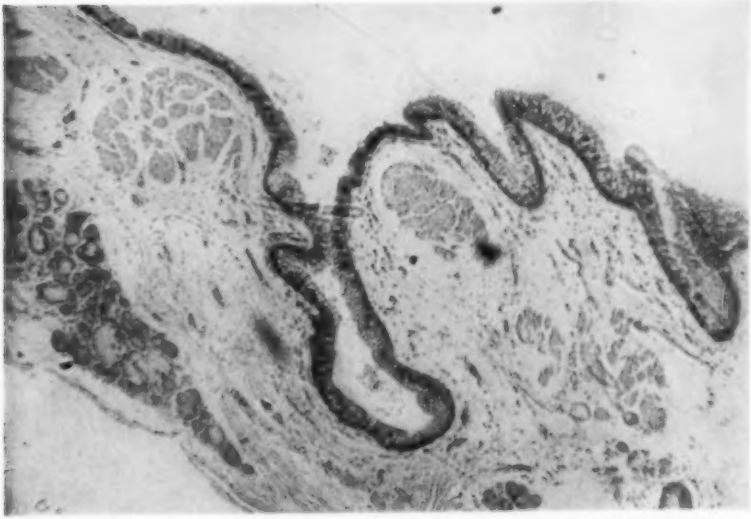

FIG. 1. Normal bronchus. Note the intact mucosa and the delicate submucosal stroma with widely scattered lymphocytes. Muscle bundles and mucous glands are present. (150×)

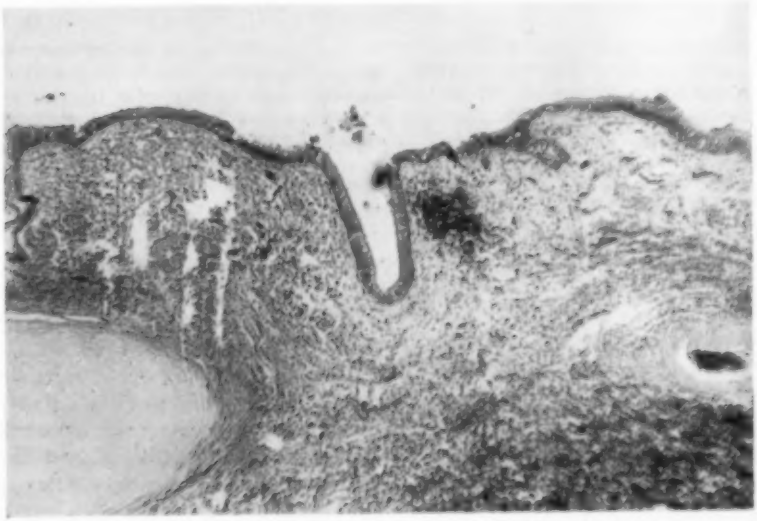

FIG. 2. Submucosal lymphocytic infiltration of bronchus. Note the intact mucosa and the moderately intense diffuse lymphocytic infiltration in the thickened submucosa. A bronchial artery and cartilage are present. (150×)

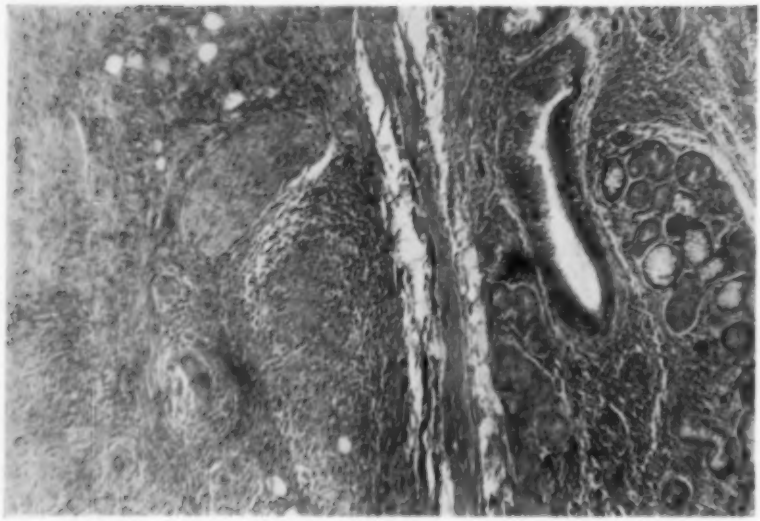

FIG. 3. Submucosal tuberculous bronchitis. Note the intense diffuse lymphocytic infiltration and the two tubercles at the left of center. The larger tubercle shows central caseation. These lesions are situated deep in the wall of the bronchus and the intact mucosa is not included. (150×)

required thoracoplasty for closure was considered as a residual space. These were included because it is believed that in at least some instances this complication occurs as a result of bronchial failure. Bronchopleural fistulas were associated with empyemas, but empyemas occurred in 2 instances without demonstrable bronchopleural fistulas. There were 19 complications in this group of 100 patients consisting of 8 residual spaces, 9 bronchopleural fistulas, and 2 empyemas. There were no spreads of the tuberculous disease in these 100 patients.

There were 41 women and 59 men, ranging in age from 11 to 61 years. The average age for the women was 31.2 years and for the men, 42.6 years.

RESULTS

Six patients had minimal pulmonary tuberculosis, 46 had moderately advanced and 48 had far advanced disease. No complications occurred in those patients with minimal disease. Of the 46 patients with moderately advanced disease, 13 per cent had postoperative complications, of which 5 were residual spaces and one a bronchopleural fistula. Of the 48 patients with far advanced disease, 27 per cent had complications consisting of 3 residual spaces, 8 bronchopleural fistulas, and 2 empyemas. Examination of the bronchus microscopically showed a greater incidence of lymphocytic infiltration and tubercle formation in those patients with moderately advanced and far advanced tuberculosis than in those with minimal disease (table 1).

Forty-seven patients had infectious sputum at the time of surgery and 53 had

TABLE 1

CLASSIFICATION OF DISEASE

	Minimal	Moderately Advanced	Far Advanced
Total cases	6	46	48
Complications			
Residual space	0	5	3
Bronchopleural fistula	0	1	8
Empyema	0	0	2
Per cent complications	0	13	27
Microscopic findings			
Normal	3	6	7
Lymphocytic infiltration	3	32	31
Tubercles	0	8	10

TABLE 2

SPUTUM

	Positive for Tubercle Bacilli	Negative for Tubercle Bacilli
Total cases	47	53
Complications		
Residual space	4	4
Bronchopleural fistula	7	2
Empyema	2	0
Per cent complications	28	11
Microscopic findings		
Normal	4	12
Lymphocytic infiltration	33	33
Tubercles	10	8

no tubercle bacilli in the sputum (table 2). Twenty-eight per cent of the patients with tubercle bacilli in the sputum had complications consisting of 4 residual spaces, 7 bronchopleural fistulas, and 2 empyemas. Those with noninfectious sputum had 4 residual spaces and 2 bronchopleural fistulas, an incidence of 11 per cent. There appeared to be no relationship between the status of the sputum with respect to tubercle bacilli and the presence of lymphocytic infiltration or tubercle formation within the bronchus. However, there were three times as many normal bronchi in the group with noninfectious sputum.

The chemotherapeutic regimens employed in this series preoperatively included streptomycin and para-aminosalicylic acid (PAS), isoniazid and PAS, or all three drugs in accepted dosages. A few patients received streptomycin alone or along with isoniazid. The series was arbitrarily divided into two groups of patients who had received chemotherapy for less than or more than eight months. Fifty-two patients (table 3) had received chemotherapy for less than eight months. Fifteen per cent of these developed complications consisting of 4 residual spaces and 4 bronchopleural fistulas. In 48 patients who had chemotherapy for longer than eight months, complications occurred in 23 per cent.

TABLE 3

CHEMOTHERAPY

	Less than 8 Months	More than 8 Months
Total cases	52	48
Complications		
Residual space	4	4
Bronchopleural fistula	4	5
Empyema	0	2
Per cent complications	15	23
Microscopic findings		
Normal	11	5
Lymphocytic infiltration	29	37
Tubercles	12	6

TABLE 4

DRUG SUSCEPTIBILITY OF ORGANISMS*

	Susceptible	Resistant
Total cases	51	9
Complications		
Residual space	4	2
Bronchopleural fistula	8	1
Empyema	2	0
Per cent complications	27.4	33
Microscopic findings		
Normal	6	1
Lymphocytic infiltration	35	5
Tubercles	10	3

* Organisms considered susceptible when inhibited by either streptomycin or isoniazid; resistant when not susceptible to either drug

There were 4 residual spaces, 5 bronchopleural fistulas, and 2 empyemas. Fewer patients had lymphocytic infiltration who had received chemotherapy for less than eight months, but the incidence of tubercle formation was approximately twice that of the patients who had received chemotherapy for more than eight months.

In 60 patients, drug-susceptibility studies were accomplished and 51 were found to have drug-susceptible organisms. Complications occurred in 27 per cent of these, with 4 residual spaces, 8 bronchopleural fistulas, and 2 empyemas (table 4). Only 9 patients were found to have resistant organisms; 3 of these patients developed complications, including 2 residual spaces and one bronchopleural fistula.

Preoperative bronchoscopic examinations were performed in 44 patients (table 5). In 30 the trachea and bronchi appeared normal. Five were considered to have tuberculous tracheobronchitis; 5, hyperemia; and 4, healed tuberculous tracheobronchitis. Microscopic sections of the bronchi considered to be normal

TABLE 5

PREOPERATIVE BRONCHOSCOPIC DIAGNOSIS

	Normal	Tuberculous Bronchitis	Hyperemia	Healed Tuberculous Bronchitis
Total cases	30	5	5	4
Microscopic findings				
Normal	5	0	1	1
Lymphocytic infiltration	19	4	3	2
Tubercles	6	1	1	1

revealed that only 5 patients had no involvement. Nineteen of the 30 showed lymphocytic infiltration and 6 had submucosal tubercles. Of the patients diagnosed bronchoscopically to have tuberculous tracheobronchitis, 4 showed inflammation and one had submucosal tubercles. Four of the 5 patients with hyperemia and 3 of the 4 with healed tuberculous tracheobronchitis demonstrated abnormal bronchi microscopically. In the 30 patients with normal bronchoscopic findings, 2 residual spaces and 6 bronchopleural fistulas occurred. In the 14 with abnormal findings, one developed an empyema.

Fifty-four patients had open cavitary disease and 46 had closed disease upon examination of the resected tissue (table 6). Twenty-six per cent of the patients with open disease developed complications, 4 of which were residual spaces; 8, bronchopleural fistulas; and 2, empyemas. Only 11 per cent of the patients with closed disease developed complications, consisting of 4 residual spaces and one bronchopleural fistula. The number of bronchi with lymphocytic infiltration was the same in both open and closed lesions, yet the finding of tubercles in the bronchial wall was twice as common in those patients with cavity.

The surgical procedures accomplished were 43 segmental resections, 35 lobectomies, 14 combined segmental resections and lobectomies, and 8 pneumonectomies (table 7). Six complications occurred among those patients treated by segmental resection consisting of 4 residual spaces and 2 bronchopleural fistulas.

TABLE 6

CAVITY

	Open Cavity	Closed Disease
Total cases	54	46
Complications		
Residual space	4	4
Bronchopleural fistula	8	1
Empyema	2	0
Per cent complications	26	11
Microscopic findings		
Normal	7	9
Lymphocytic infiltration	35	31
Tubercles	12	6

TABLE 7

SURGICAL PROCEDURE

	Segmental Resections	Lobectomies	Segmental Resections and Lobectomies	Pneumonectomies
Total cases	43	35	14	8
Complications				
Residual space	4	3	1	0
Bronchopleural fistula	2	4	1	2
Empyema	0	0	0	2
Microscopic findings				
Normal	4	9	1	2
Lymphocytic infiltration	31	19	11	5
Tubercles	8	7	2	1

TABLE 8

MICROSCOPIC FINDINGS IN BRONCHUS

	Normal	Inflammation	Tubercle
Total cases	16	66	18
Complications			
Residual space	0	7	1
Bronchopleural fistula	0	6	3
Empyema	0	2	0
Per cent complications	0	22.7	22.2

Three residual spaces and 4 bronchopleural fistulas occurred after lobectomy. In the combination of segmental resection and lobectomy, one patient had a residual space and one a bronchopleural fistula. Of the 8 patients treated by pneumonectomy, 2 developed bronchopleural fistulas and 2, empyemas.

In correlating the microscopic findings in the bronchus with the complications (table 8), it was found that no complication occurred in any patient with a normal bronchus at the point of transection. There were 22.6 per cent complications among the 84 patients with abnormal bronchi; 15 occurred in those patients with lymphocytic infiltration and 4 in those with submucosal tubercles.

The complications in patients whose bronchi showed lymphocytic infiltration were: residual space in 7, bronchopleural fistula in 6, and empyema in 2. Of the patients with tubercles in their bronchi, one developed a residual space and 3 had bronchopleural fistula. Two of the 100 bronchi examined showed ulceration and both were associated with submucosal tubercles. One of the latter patients developed an empyema.

DISCUSSION

Bronchopleural fistulas and empyemas represent serious complications in the resectional treatment of pulmonary tuberculosis. Day and associates (9) found an incidence of 13 per cent of bronchopleural fistulas with empyema in 202 patients treated by resection. Mulvihill (10) states that in 128 resections for

pulmonary tuberculosis bronchopleural fistulas occurred in 13 patients. In 1954, Decker and his co-workers (11) observed that following 463 operative procedures performed on 373 patients with pulmonary tuberculosis there occurred 14 spaces requiring thoracoplasty, 59 transient bronchopleural fistulas requiring closed drainage, 3 bronchopleural fistulas treated by thoracotomy, and 2 bronchopleural fistulas associated with tuberculous empyema. Gordon (12) found that bronchopleural fistulas occurred in 50 per cent of 28 patients treated by resection who had not received streptomycin prior to the surgical procedure, while in 79 patients who received some streptomycin prior to operation bronchopleural fistulas occurred in 16 per cent. This writer suggested that tuberculous lesions in the bronchial stump probably are important in the development of bronchopleural fistulas. During 1955 at the Ohio Tuberculosis Hospital, the incidence of bronchopleural fistula and empyema was 3.5 per cent.

The finding of active tuberculous tracheobronchitis has been considered by some surgeons as a contraindication to resection (13, 14). As experience was gained with chemotherapy for tuberculosis, it became apparent that one of its effects was early healing of the trachea and bronchi (15, 16). Recent observations have shown that, despite mucosal healing of the tracheobronchial tree following chemotherapy, in many cases a submucosal inflammatory reaction remains. Olson and associates (17), in examining the resected bronchi of 602 surgical specimens, found that only 10 per cent were normal, 29 per cent showed evidence of chronic bronchitis, and 20 per cent showed tuberculous bronchitis. The remainder of the specimens revealed bronchial abnormalities related to bronchiectasis. Hardy and Sampson (18) have also noted the tendency of antituberculous chemotherapy to produce epithelial healing of the bronchial tree while submucosal and mural lesions persist. While Olson and his group made no attempt to correlate the findings in the bronchus with complications, Hardy and Sampson suggested that these microscopic findings have no relationship to the development of complications. This opinion has been suggested previously (19, 20).

Examination of the data from the present study indicates that those patients with moderately or far advanced tuberculosis, with open cavities, and with infectious sputum have a greater incidence of complications than those with minimal disease, closed disease, or noninfectious sputum. While those patients who received chemotherapy for eight months or less had fewer complications than those who received drugs for longer periods, this probably reflects the fact that many of the patients who received prolonged therapy were more seriously ill than those who received therapy for shorter periods. The susceptibility or the resistance of the tubercle bacilli to the drugs used appeared to have little relationship to the incidence of complications in these cases.

Fourteen per cent of the 43 patients subjected to segmental resection developed complications, as did 14 per cent of 14 patients in whom segmental resection and lobectomy were accomplished simultaneously. Lobectomy in 35 patients was followed by complications in 20 per cent; and pneumonectomy in 8 patients by complications in 50 per cent. While the incidence of complications

in the latter group appears to be out of proportion to the other three groups of surgical procedures, perhaps the small number of cases gave an abnormally high percentage of complications.

The correlation between bronchoscopic and microscopic findings was higher when the tracheobronchial tree was found to be abnormal than when it was normal. This reflects the fact that at bronchoscopy only the mucosa is visualized and that this does not always reveal the condition of the underlying tissue.

The most significant aspect of this study is in the correlation of the postoperative complications with the microscopic findings in the resected bronchus. No patient found to have a normal bronchus microscopically developed a postoperative complication. Twenty-three per cent of the 66 patients showing lymphocytic infiltration developed some postoperative complication, as did 22 per cent of the 18 patients in whom submucosal tubercles were found. This would suggest that the presence of increased lymphocytic infiltration in the submucosal area of the bronchus is as significant in the development of postoperative complications as the finding of specific tubercles.

Hardy and Sampson (18) have stated that postoperative complications occur only in the presence of active disease of the bronchial mucosa. It would appear from the present observations that this may be an oversimplification of the situation. The great majority of the bronchi studied would fulfill the Hardy-Sampson criteria for the "quiescent bronchus," since only 2 patients showed evidence of mucosal ulceration microscopically. Despite this, 19 patients with submucosal involvement developed postoperative complications. It is suggested that the condition of the tissue underlying the mucosa does play a part in the process of healing after surgical transection. While in many patients showing either lymphocytic infiltration or submucosal tubercles healing may occur per primum, it is stressed that this cannot be expecte uniformly. To further evaluate this observation, a study is in progress to relate pre-resection bronchial biopsies to the results of local treatment, microscopic findings in the transected bronchus, and postoperative complications.

SUMMARY

The cases of 100 patients subjected to resectional surgery between 1951 and 1955 have been reviewed clinically and pathologically in an effort to relate the condition of the transected bronchus to the incidence of postoperative complications. A greater incidence of complications occurred in those patient with moderately advanced or far advanced disease, in those with open cavity, and in patients with sputum positive for tubercle bacilli. There was also a higher incidence of complications in the patients who received chemotherapy for longer than eight months. Preoperative bronchoscopic observations correlated poorly with microscopic findings except when abnormal mucosa was seen.

No complication occurred in the patients with normal transected bronchi, while 23 per cent of the patients who showed lymphocytic infiltration and 22 per cent of those with submucosal tubercles developed complications. This suggests that the finding of lymphocytic infiltration is as important in relation to development of postoperative complications as the demonstration of actual

tubercles within the bronchial wall. Furthermore, these lesions may be as important as the presence of more advanced disease, open cavity, or sputum positive for tubercle bacilli in relation to postoperative occurrence of residual pleural space, bronchopleural fistula, and empyema.

SUMARIO

La Correlación de la Patología del Bronquio Reseccionado con las Complicaciones Postoperatorias en la Tuberculosis Pulmonar

Los protocolos de 100 enfermos sometidos a la resección quirúrgica entre 1951 y 1955 han sido repasados clínica e histopatológicamente tratando de relacionar el estado del bronquio transeccionado con la incidencia de complicaciones postoperatorias. Esta incidencia fué mayor en los sujetos que padecían de enfermedad moderadamente avanzada o muy avanzada, en los que tenían cavernas abiertas y en aquéllos cuyo esputo era positivo para bacilos tuberculosos. La incidencia de complicaciones fué también mayor en los enfermos que recibieron quimioterapia por más de ocho meses. Las observaciones broncoscópicas preoperatorias correlacionaron muy poco con los hallazgos microscópicos, excepto cuando se observó una mucosa anómala.

No hubo complicaciones en los enfermos cuyo bronquio transeccionado era normal, en tanto que las manifestaron 23 por ciento de los que revelaron infiltracón linfocitaria y 22 por ciento de los que tenían tubérculos submucosos. Esto sugiere que el hallazgo de infiltración linfocitaria es tan importante en relación con la aparición de complicaciones postoperatorias como el descubrimiento de verdaderos tubérculos dentro de la pared bronquial. Además, esas lesiones pueden revestir tanta importancia como la presencia de enfermedad más avanzada, cavernas abiertas o esputo positivo para bacilos tuberculosos in relación con la ocurrencia postoperatoria de espacio pleural residual, fístula broncopleural y empiema.

RESUME

Corrélation entre l'histo-pathologie de la bronche réséquée et les complications post-opératoires dans la tuberculose pulmonaire

Les observations de 100 malades soumis à la chirurgie d'exérése entre 1951 et 1955 ont été passées en revue du point de vue clinique et pathologique, dans le but d'établir un rapport entre l'état de la bronche réséquée et l'incidence des complications post-opératoires. Une fréquence plus grande des complications s'est manifestée chez les malades dont le degré de la tuberculose était modérément ou très avancé, chez ceux porteurs de cavernes ouvertes et les malades dont les crachats étaient positifs pour le bacille tuberculeux. Il existait également une incidence plus élevée des complications chez les malades qui étaient soumis à la chimiothérapie pendant plus de 8 mois. Les observations bronchoscopiques préopératoires ne concordaient pas bien avec les résultats de l'examen histologique, sauf lorsqu'une altération de la muqueuse était observeé.

Aucune complication n'est survenue chez les malades dont les bronches réséquées étaient normales, tandis que 23% des cas où existait une infiltration lymphocytaire, et 22% des cas avec tuberculomes sous-muqueux présentèrent des complications. Ceci suggère que la découverte d'une infiltration lymphocytaire est aussi importante à l'égard du développement de complications post-opératoires que la démonstration de tuberculomes dans la paroi bronchique. De plus, ces lésions peuvent être aussi importantes que l'existence d'une tuberculose de degré avancé, de cavernes ouvertes ou de crachats «positifs» en ce qui concerne la cavité pleurale résiduelle, les fistules broncho-pleurales et l'empyème post-opératoires.

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DIFFERENTIAL DIAGNOSIS BETWEEN BERYLLIUM POISONING AND SARCOIDOSIS[1-3]

HARRIET L. HARDY

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INTRODUCTION

There are several good reasons for summarizing current knowledge of diagnostic differences between the disease following exposure to certain beryllium compounds and the clinical entity, sarcoidosis. In the first place, roentgenographic study of the chest has revealed a number of cases of miliary densities in patients without symptoms which may be a manifestation of either beryllium disease or sarcoidosis, and these cases offer a real problem in diagnosis. In addition, because the present outlook is less favorable in chronic beryllium poisoning than in Boeck's sarcoid, definitive diagnosis is important. Furthermore, if we are to increase knowledge of the epidemiology and clinical character of both diseases, it is essential that each case should be correctly classified. Finally, for social and economic reasons, in fairness to patient and industry, job-related beryllium disease must be accurately diagnosed.

TERMINOLOGY

To make this discussion as helpful as possible the terminology used is clearly defined. The title "sarcoidosis" or "Boeck's sarcoid" is used to indicate a clinical entity which has been described by medical writers whose names are well known (1, 2). The term "sarcoid" will be used when a histopathologic picture only is being discussed.

Disease associated with exposure to toxic beryllium compounds documented by epidemiologically sound data or tissue assay plus a granulomatous reaction is here called "beryllium disease" or "beryllium poisoning" (table 1). Current epidemiologic knowledge leads to the conclusion that in some persons disease follows the inhalation of unknown doses of beryllium metal, some alloys of beryllium with other metals, certain beryllium oxides, and acid salts of beryllium, especially the fluoride and the sulfate. Berylore does not, as far as is known, produce illness (table 2).

Collected autopsy material has established that beryllium can produce lesions in liver, spleen, kidney, myocardium, lymph nodes, pleura, and lung. Laboratory studies of patients demonstrate disturbance in nitrogen and calcium metabolism, disturbed liver function, and an increase in serum protein with a relative increase in gamma globulin. From these data, it seems clear that toxic beryllium compounds produce a systemic disease which may best be called "beryllium disease" or "beryllium poisoning." The term "pulmonary granulomatosis of beryllium workers" should be dropped from usage. This term was adopted informally by the Saranac Symposium of 1947 before present knowledge of

[1] From the Massachusetts General Hospital, Boston, Massachusetts.

[2] Presented, in part, before the Medical Session, as part of *Section 1A*, at the annual meeting of the National Tuberculosis Association, New York, New York, May 21, 1956.

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TABLE 1

TERMINOLOGY

Most workable	
Beryllium disease	
Beryllium poisoning (acute or chronic)	
Too narrow (pathologic designation)	
Pulmonary granulomatosis of beryllium workers (Saranac Symposium, 1947)	
Confusing	
Berylliosis—correct spelling (from beryllium)	
Berylosis, Beryllosis	incorrect spelling (derived from beryl or omitting crucial "i")

TABLE 2

TOXIC AND NONTOXIC BERYLLIUM COMPOUNDS

Beryllium (Be, the element)	
Beryllium metal, Beryllium oxides, Certain beryllium salts	disease producing
Beryl ($3BeO \cdot Al_2O_3 \cdot 6SiO_2$—the ore)	
Not disease producing	

systemic manifestations of beryllium poisoning was available. Such a term, reflecting description of a pathologic process and confining disease to one-organ involvement, is limited in its usefulness in delineating what is a new disease of protean manifestations still unfolding its clinical character.

Engineering protection has practically eliminated cases of the acute phase of beryllium poisoning so well described by Van Ordstrand and associates in 1945 (3). Cases of acute beryllium reaction on record describe an acute pneumonitis, easily mistaken for viral pneumonia. Less serious reaction to beryllium salts is irritation of skin and mucous membranes of the upper respiratory tract. In patients living over a period of weeks with acute beryllium pneumonitis, changes in gamma globulin and cellular reaction in liver and lung suggest that the acute as well as the chronic disease is systemic and these two conditions comprise one entity.

The term "berylliosis," although accurate, is deliberately not used in this discussion because there has been such confusion in its spelling and definition. This point is labored because the most recent edition of *Standard Nomenclature* (4) uses the spelling "beryllosis" and classifies the disease as a chemical intoxication. The Greek word for beryl is *beryllos*—hence the word beryllosis, suggesting that disease follows exposure to beryl ore. The ore has thus far proved harmless. Industry extracts the element, beryllium, from beryl by complicated chemical operations and it is certain compounds of beryllium that have proved toxic. The *New Gould Medical Dictionary* (5) defines berylliosis as "a pneumoconiosis due to inhalation of beryllium oxide dust." Since beryllium compounds are taken into the body as a fume and may produce lesions remote from the lung, the mechanism of disease production is comparable to a chemical intoxication such as lead poisoning rather than a pneumoconiosis like silicosis. Because the lung is so regularly damaged in beryllium disease in contrast to the erythrocyte in lead intoxication, the present confusion in the literature is understandable. The present discussion will concern itself with chronic beryllium poisoning which mimics sarcoidosis.

CLINICAL FINDINGS

The similarity of the clinical pictures presented by beryllium disease and sarcoidosis is striking. With variation in onset, patients with both diseases complain of increasing fatigue, weakness, anorexia, weight loss, dyspnea, chest pain, and cough. A number of patients with either chronic beryllium poisoning or sarcoidosis first come for medical evaluation after routine chest roentgenographic surveys in communities or industrial plants have brought to light miliary densities in both lung fields, although the patient has no symptoms or signs of illness. At some stage in both diseases, examination may reveal clubbed fingers; an enlarged liver or spleen; abnormal auscultatory findings, pneumothorax, emphysema; right heart enlargement with or without failure. A variety of skin lesions may occur in both diseases. The small, discrete, elevated nodules or flat plaques with a scaly surface are more often seen in beryllium disease than the large conglomerate masses described in series of sarcoidosis in which Negroes predominate. Biopsy of such lesions in the industrially related disease reveals a sarcoid reaction, and beryllium is found to be present. Both beryllium poisoning and sarcoidosis may show the following abnormalities: bromsulphalein retention and other evidence of disturbed liver function, increase in total serum protein with related increase in globulin, occasional hypercalcemia and hypercalcuria (1, 6, 7). Both diseases may cause renal calculi.

COURSE

A long course of illness with remission and exacerbation may characterize either chronic beryllium poisoning (8) or sarcoidosis (1). Death is usually occasioned in both instances by myocardial failure or overwhelming loss of functioning lung tissue, with or without pneumothorax, due to rupture of emphysematous bullae. Lung function studies show a defect in the exchange of gases across the alveolar membrane as the basis for producing symptoms in both diseases, with loss of elasticity in severe cases and those of long duration.

PATHOLOGIC FINDINGS

In both Boeck's sarcoid and beryllium disease the pathologic reaction is granulomatous with subsequent replacement of granulomata by nonfunctioning fibrous tissue.

DIFFERENCES BETWEEN BERYLLIUM DISEASE AND SARCOIDOSIS

A registry of cases of beryllium disease in the United States has been set up at the Massachusetts General Hospital. Through the courtesy of private and industrial physicians, just over 500 case records have been produced and are now on Keysort cards for study. These 500 cases have two things in common: a convincing beryllium exposure revealed by epidemiologic study and/or evidence of beryllium in tissue or urine; and respiratory tract disease. From such data and the writer's own clinical experience, certain differences between beryllium disease and sarcoidosis can be summarized.

No ocular lesions, such as iritis and uveitis, so frequently reported in series of cases of sarcoidosis have been reported in beryllium poisoning. In beryllium disease, there are no cases which present roentgenographic evidence of hilar node enlargement without densities in the lung field. Clinically, cervical or axillary node enlargement is rare; hilar node enlargement is present but not striking. In autopsied cases, hilar, abdominal, and pelvic adenopathy is regularly reported. No parotid or tonsillar lesions have yet been described in beryllium poisoning. The striking cystic bone changes seen roentgenographically in a small percentage of cases of sarcoidosis are not seen in the man-made disease but, on special search, the long bones are found to be denser than normal.

A striking difference between sarcoidosis and beryllium disease is the prognosis both as to morbidity and mortality. Patients with sarcoidosis may completely recover. This is not true of patients with chronic beryllium poisoning. There are instances of spontaneous remission in the man-made disease, but chest film changes and some respiratory disability remain. One of the writer's patients with chronic beryllium poisoning, having received steroid therapy for nearly three years, eventually showed clearing of the marked roentgenographic changes, with relief of symptoms. Withdrawal of the drug resulted in a return of smaller visible densities but few symptoms. This suggests that further experience may have results very different from those that can now be reported.

The use of steroids has changed the outlook for patients with beryllium disease, but has resulted in no true cures (7). The patients are more comfortable on adequate doses of these drugs, and follow-up lung function studies demonstrate that there is measurable improvement in the diffusion defect. In contrast, the effect of steroid therapy on patients with sarcoidosis, who have been treated before marked pulmonary fibrosis is established, is dramatic in some cases. As many have pointed out, this is hard to evaluate because of the known spontaneous cure of this disease. At present, there is good evidence that the prognosis is better, both as to morbidity and mortality, in sarcoidosis than in beryllium disease. Further, in the writer's experience, perhaps because of the above-stated prognosis, the response to therapy with steroid preparations, while definite in both diseases, has been more satisfactory in sarcoidosis. These conclusions must be opinions at present because our knowledge of both diseases is constantly changing, and there can be no question but that the clinical character of the beryllium-induced disease and sarcoidosis varies in different groups of cases seen in different parts of this country and abroad.

CUTANEOUS REACTIONS TO VARIOUS ANTIGENS

Skin testing must be done in every case of suspected beryllium disease or Boeck's sarcoid in the attempt to exclude the presence of histoplasmosis and coccidioidomycosis. Urbach and co-workers (9) have shown that depressed reactivity to several usually antigenic materials is characteristic of sarcoidosis, perhaps accounting for the high incidence rate of negative sensitivity to tuberculin. In contrast to sarcoidosis, reaction to tuberculin testing in cases of beryllium poisoning in the Massachusetts General Hospital series has not resulted in re-

sponses strikingly different from those of the general population. Not all observers have had uniform experience with a positive Nickerson-Kveim reaction (10–12) as evidence of sarcoidosis. In a few of the writer's cases of beryllium disease, in which this test was tried, the response was considered a nonspecific foreign-body reaction.

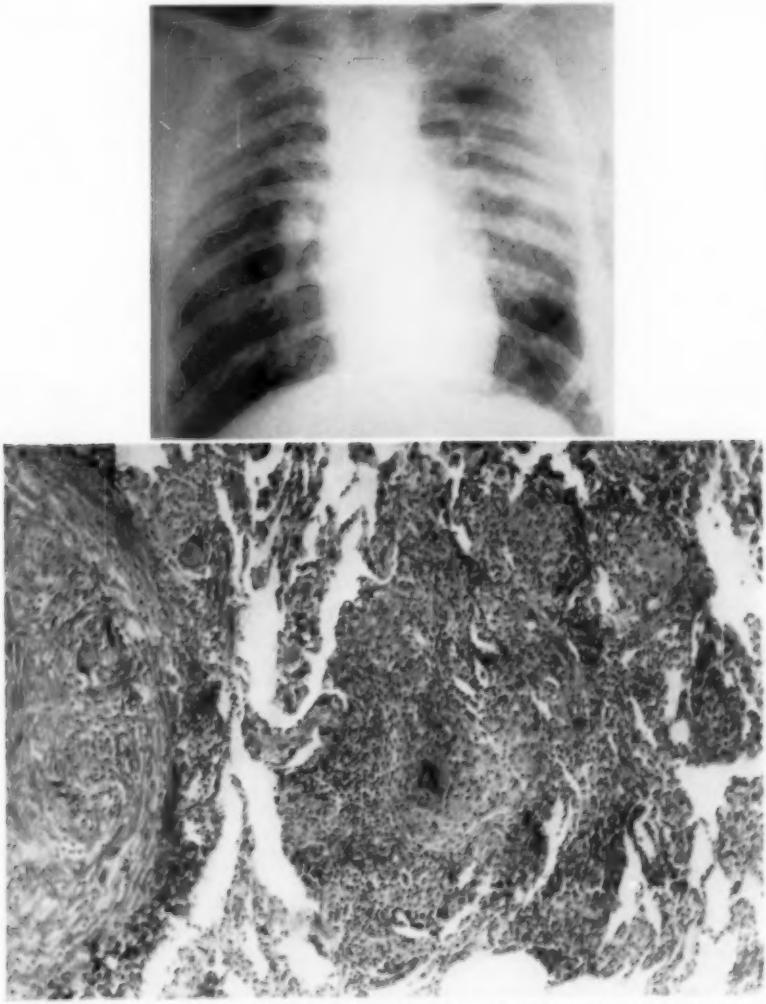

FIG. 1. Chest roentgenogram (top) and photomicrograph of lung biopsy (bottom) of a fluorescent lamp manufacturing worker with a diagnosis of miliary tuberculosis, then Boeck's sarcoid, and finally beryllium disease.

Curtis (13) has reported that patch tests done with small amounts of inorganic beryllium salts are positive in patients with beryllium disease. Since beryllium is known to be a skin sensitizer, some question arises concerning the usefulness of a positive patch test in a patient known to have been repeatedly exposed to

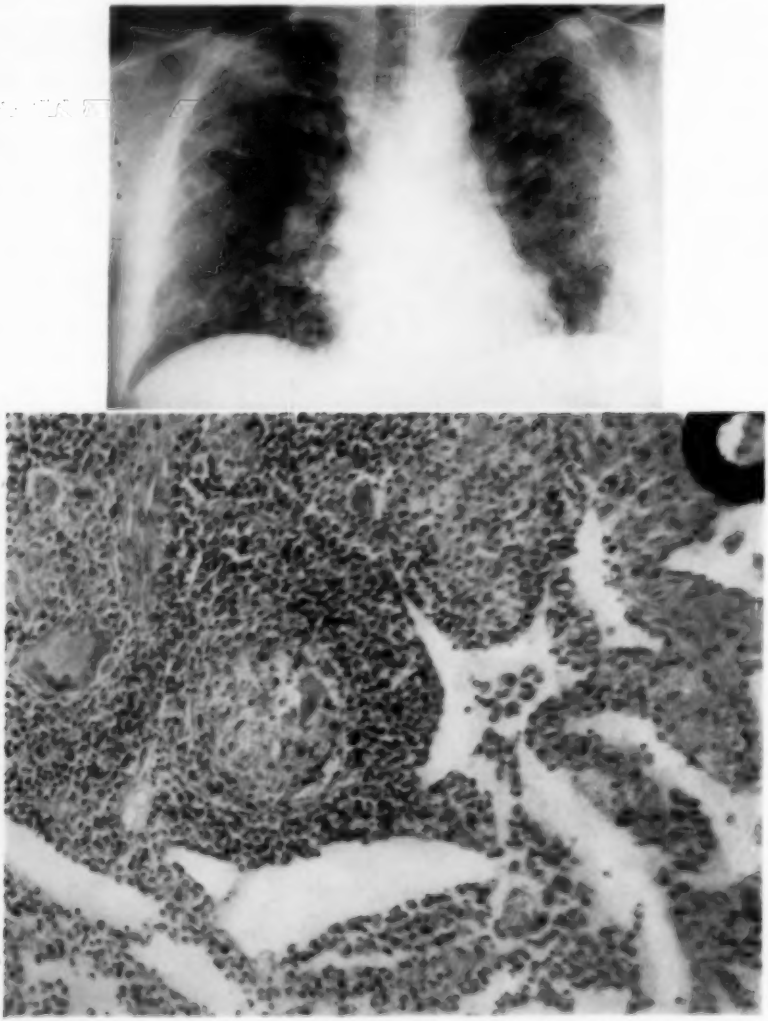

FIG. 2. Chest roentgenogram (top) and photomicrograph of lung biopsy (bottom) of a draftsman in a fluorescent lamp manufacturing plant with a diagnosis of asthma, polycythemia vera, and idiopathic pulmonary fibrosis before the final diagnosis of beryllium poisoning.

air-borne beryllium compounds. More experimental work and clinical studies must be done to follow up Curtis' important observation. In the writer's opinion, from experience and study of the literature, skin testing in a variety of ways may provide suggestive, but not final, negative or positive evidence in making a differential diagnosis between the chemically-induced disease and Boeck's sarcoid.

The chest film, then, is the usual means of raising the question of, and at the

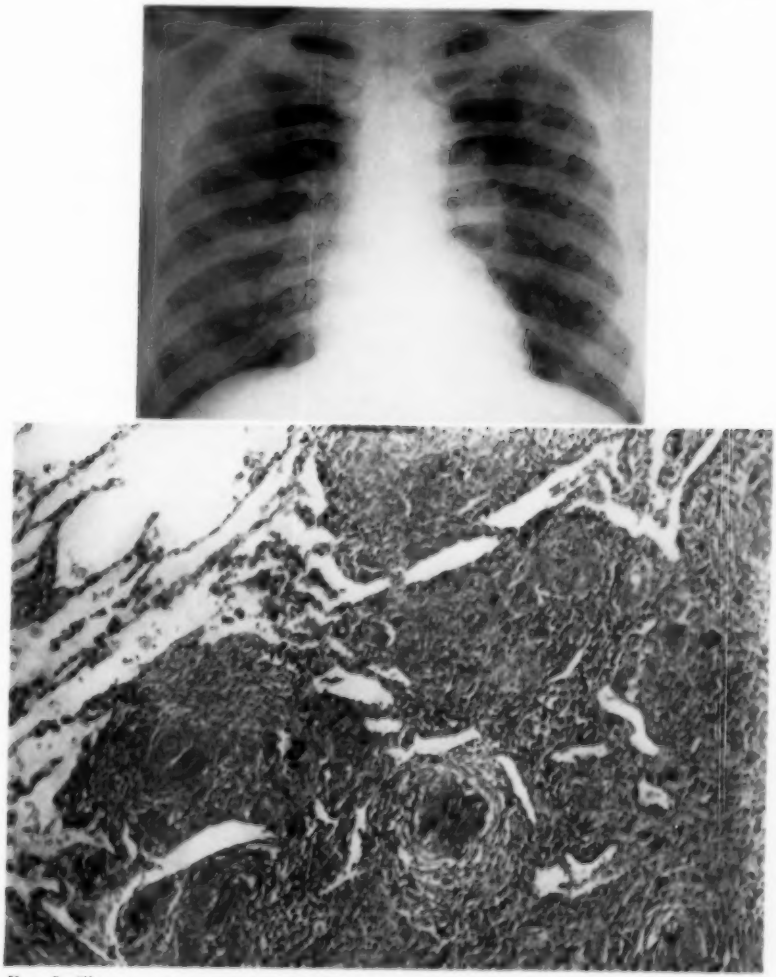

FIG. 3. Chest roentgenogram (top) and photomicrograph of lung biopsy (bottom) of a young man with a diagnosis of miliary tuberculosis and then Boeck's sarcoid.

same time confusing, these two diagnoses. In each case, miliary tuberculosis, Hodgkin's disease, fungal infections, carcinomatosis, erythema nodosum, siderosis, and silicosis must be considered. Less likely possibilities, such as eosinophilic pneumonia or hemosiderosis, may prove to be the true diagnosis.

ILLUSTRATIVE CASES

Four examples of beryllium disease are illustrated in figures 1–4.

The pathologic findings in the biopsy material obtained in these 4 cases bear

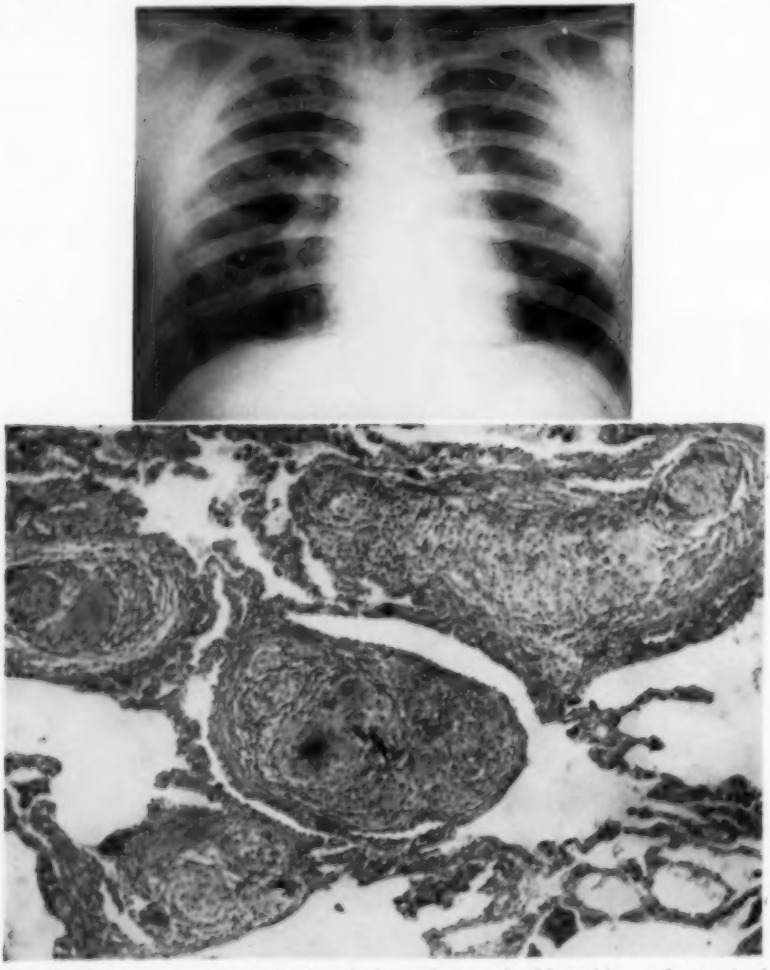

FIG. 4. Chest roentgenogram (top) and photomicrograph of lung biopsy (bottom) of a metallurgist with an original diagnosis of beryllium disease and, after lung biopsy showed no beryllium in tissue, a diagnosis of sarcoidosis.

TABLE 3

INCRIMINATED BERYLLIUM-USING OPERATIONS

Extraction of beryllium	Beryllium metallurgy
Fluorescent powder manufacturing	Ceramic operations
Fluorescent lamp manufacturing	Radio tube manufacturing
Fluorescent lamp salvage	Atomic energy development
Neon sign manufacturing	Neighborhood contamination
Beryllium alloy manufacturing	Use of alloys containing more than 4 per cent beryllium

out the thesis of nonspecificity and variation in exact picture within the general classification of granulomatous reaction. However, Schepers (14) and Nickerson (15) believe it is possible to distinguish on histologic grounds alone the difference between Boeck's sarcoid and beryllium poisoning. Castleman (16) and his associates, and Hazard (17) consider that it is not possible in most cases to make the differential diagnosis on pathologic evidence alone.

PREVALENCE OF POTENTIAL BERYLLIUM HAZARDS

Knowledge of prevalence of a disease is useful in making correct diagnoses. In considering a diagnosis there is reliable information on industrial operations that result in a potential beryllium hazard (8). This list may grow as knowledge increases (table 3).

The number of workers or their neighbors exposed to toxic beryllium compounds is not now known. Furthermore, because there may be a delay of longer than ten years from cessation of exposure to illness, there are no reliable data of incidence rates of beryllium disease for any particular industry. Almost every state in the union has reported cases of beryllium poisoning.

REACTION OF SARCOIDOSIS TO GEOGRAPHIC LOCALITY

The studies of Michael and co-workers (18) and Gentry and associates (19) draw attention to the striking relationship between sarcoidosis and residence in certain parts of the United States, with common environmental factors which may have a bearing on etiology. The increase in prevalence of sarcoidosis in the Negro population over the white, previously reported, was again noted. The report of finding traces of beryl, industry's source of beryllium, in the soil on which the majority of Gentry's patients with sarcoidosis live is of great interest. Cummings and colleagues (20), studying 1,194 cases of sarcoidosis, found that patients with the disease live in nonarid, tree-growing areas of the United States. They plan studies to elucidate possible etiologic factors arising from this knowledge of residence. While the studies of groups of sarcoidosis cases in the literature give no exact knowledge of the total number of cases in a given community, they do sustain the current belief that the chance that an individual exposed to toxic beryllium compounds will also suffer from sarcoidosis is remote indeed. The fact that, to date, no beryllium has been found in biopsy or autopsy material in cases of sarcoidosis further supports the belief that the differential diagnosis between beryllium disease and Boeck's sarcoid can be accurately made.

It is useful to know that beryl is found in small amounts in certain coal fields. As a result, it has been found in coal miners' lungs when looked for by spectrographic analysis. However, the coal miners' lungs do not show granulomatous pathologic change; nor do the lungs of inhabitants of one city (21) where the air is known to be contaminated with traces of beryl. It is believed that beryllium is locked tight in beryl as it occurs in nature and only after the element is extracted is it pathogenic.

* * *

What, then, are the criteria of real reliability in making a satisfactory differential diagnosis between sarcoidosis and beryllium poisoning? It is believed, on the basis of present knowledge, that sarcoidosis and beryllium disease are differentiated, in the last analysis, by discovery through spectrographic or chemical means of beryllium in tissue showing granulomatous lesions. Knowledge of epidemiologic distribution of sarcoidosis and incriminated industrial operations using beryllium is helpful. At present, sarcoidosis has a more benign prognosis than beryllium disease. As far as is known, ocular, tonsillar, and parotid lesions, and cystic bone changes of sarcoidosis have not been seen in beryllium poisoning. It is not possible to make a correct differential diagnosis with chest roentgenographic changes or histopathologic reaction as the criteria.

As in most medical diagnoses, the final decision prior to the privilege of autopsy arises from more than one finding. Occupational history, clinical course, chest roentgenographic picture, and biochemical abnormalities are important. The diagnosis of chemically induced granulomatous disease is established by finding beryllium in pathologically involved tissues. This often leaves sarcoidosis —as it was before beryllium disease was recognized—a diagnosis by exclusion.

SUMMARY

The reasons for discussing the differential diagnosis between beryllium poisoning and sarcoidosis are as follows: Routine chest roentgenographic surveys, discovering persons without symptoms but showing miliary roentgenographic densities, create diagnostic problems. As the course of beryllium disease is less favorable than that of sarcoidosis, knowledge of the difference between the two diseases is important. As cases of both diseases continue to appear, increase in knowledge of their clinical character can only be arrived at if diagnostic criteria are agreed upon. Finally, for social and economic reasons, it is important that job-related beryllium disease be identified. Because of biochemical abnormalities and involvement of the liver, spleen, kidney, and myocardium, as well as the lung, beryllium poisoning is considered a systemic intoxication. The term "berylliosis" is confusing because of variation in the spelling (such as berylosis), which suggests that the disease is a pneumoconiosis. When spelled "berylosis" the implication is that beryl ore can cause disease, which is not the case. The final diagnosis cannot be made by chest roentgenogram and pathologic means but by finding beryllium in granulomatous tissue.

SUMARIO

El Diagnóstico Diferencial entre el Envenenamiento por Berilio y la Sarcoidosis

Las siguientes son las razones para discutir el diagnóstico diferencial entre el envenenamiento por berilio y la sarcoidosis:[1] Las corrientes encuestas radiográficas del tórax, al descubrir individuos asintomáticos, pero que revelan condensaciones miliares en las películas, crean problemas de diagnóstico. Como la evolución de la beriliosis es menos favorable que la de la sarcoidosis, es importante conocer la diferencia entre las dos dolencias. Como continúan apareciendo casos de ambas afecciones, sólo puede alcanzarse un conocimiento mejor de su naturaleza clínica si se conviene en las pautas de diagnóstico. Por fin, por razones sociales y económicas, es importante que se identifique la beriliosis enlazada con la ocupación del sujeto. Debido a las anomalías bioquímicas y a la invasión del hígado, bazo, riñón y miocardio, la beriliosis está considerada como envenenamiento orgánico. El término de "beriliosis" ocasiona confusión debido a variaciones ortográficas (por ej., berilosis), que sugieren que la enfermedad es una neumoconiosis. Cuando se la llama "berilosis", la connotación es que la mena del berilio puede provocar enfermedad, lo cual no es cierto. No cabe hacer el diagnóstico definitivo con radiografías torácicas y estudios histopatológicos, pero sí descubriendo berilio en el tejido granulomatoso.

RESUME

Diagnostic différentiel entre l'intoxication par le Béryllium et la Sarcoidose

Les raisons d'une discussion sur le diagnostic différentiel entre l'intoxication par le béryllium et la sarcoidose sont les suivantes; le dépistage radiologique systématique qui découvre des individus dépourvus de symptômes, mais présentant des opacités miliaires crée des problèmes diagnostiques. Comme l'évolution de l'intoxication par le béryllium est moins favorable que le cours de la sarcoidose, la connaissance de la différence entre ces deux affections est importante. A mesure que des cas de ces deux affections continuent à apparaître, l'accroissement des données sur leurs caractéristiques cliniques ne sera atteint que par l'établissement de critères diagnostiques. Enfin, pour des raisons sociales et économiques, il est important que la maladie professionnelle due au béryllium soit identifiée. A cause des altérations biochimiques, des lésions du foie, de la rate, du rein et du myocarde ainsi que du poumon, l'intoxication par le béryllium est considérée comme une intoxication générale de l'organisme. Le terme "béryllose" prête à confusion à cause de la variation de son orthographe (telle que béryliose) qui risque d'indiquer qu'il s'agit d'une pneumoconiose. Quand on l'écrit "béryliose" cela implique la participation du minéral béryl dans l'étiologie de l'affection, ce qui n'est pas le cas. Le diagnostic définitif ne peut être acquis par la radiologie thoracique ou par d'autres moyens que la découverte du béryllium dans les tissus du granulome.

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U. S. VETERANS ADMINISTRATION-ARMED FORCES COOPERATIVE STUDIES OF TUBERCULOSIS[1,2]

V. Antimicrobial Therapy in the Treatment of Primary Tuberculous Pleurisy with Effusion: Its Effect upon the Incidence of Subsequent Tuberculous Relapse

ABRAHAM FALK AND WILLIAM W. STEAD

(Received for publication May 22, 1956)

INTRODUCTION

In 1951 it was recommended, on the basis of the Veterans Administration-Armed Forces Study of the therapy of tuberculosis, that all cases of primary tuberculous pleurisy with effusion (idiopathic pleurisy with effusion) be treated with antimicrobial therapy, as well as by sanatorium care. Recognizing that pleurisy with effusion represents tuberculosis with a high rate of subsequent relapse in the five years following the onset of the effusion, it was believed that every effort should be made to reduce the incidence of relapse. The series reported by Roper and Waring (1) with a 65 per cent relapse rate within the first year after the onset of the effusion is a striking example of the clinical significance of this manifestation of tuberculosis. The present paper is a report of the results of the cooperative study to January 1, 1956.

PLAN OF STUDY

In addition to the treated series, it was also possible to obtain information on a series of cases in which antimicrobial therapy had not been used. The series for comparison comprise 382 patients who received various periods of chemotherapy and 209 who received no chemotherapy. All patients in both series were hospitalized. However, the treated and untreated series were not concurrent in time, nor was there randomization in selection for chemotherapy against untreated controls.

The criteria (2) established for selection of cases were:

> The effusion should be of recent origin, preferably not extending over sixty days. The tuberculin skin reaction should be definitely positive before or during treatment. Tubercle bacilli should, when possible, be demonstrated in the aspirated fluid by culture or guinea pig inoculation, either at the time of beginning therapy or subsequent thereto.
>
> Prior to treatment, every effort should be made to exclude a nontuberculous etiology of the effusion.
>
> Patients having a demonstrable parenchymal lesion at the onset of the effusion were excluded from the study.

[1] From the Pulmonary Disease Service, Veterans Administration Hospital, Minneapolis, Minnesota.

[2] Presented before the Medical Session, as part of *Section 4*, at the annual meeting of the National Tuberculosis Association, New York, New York, May 22, 1956.

OBSERVATIONS

The background factors in both series were remarkably similar. Approximately half of the patients in each series were less than thirty years of age, 95 per cent in each series were males, and approximately two-thirds of each group were white. The two sides of the chest were equally affected in each group. None of the patients in either group had roentgenographic evidence of intrapulmonary lesions at the beginning of hospital treatment.

Antimicrobial therapy was not uniform as to the agents used or the duration of therapy. There were 16 patients who received chemotherapy for less than four months, chiefly streptomycin alone. However, more than half the patients received chemotherapy for six months or more with various combinations of antimicrobial agents.

The total rate of tuberculous complications, excluding recurrent effusion, was 19 per cent in the untreated group and 4 per cent in the group which received chemotherapy (table 1).

Pulmonary tuberculosis was the most frequent complication in each group and skeletal tuberculosis was the most frequent extrapulmonary complication. Renal tuberculosis was reported in only one case.

Two deaths were attributable to a tuberculous relapse, both occurring in the

TABLE 1

INCIDENCE OF TUBERCULOUS COMPLICATIONS FOLLOWING THE ONSET OF TUBERCULOUS PLEURAL EFFUSION

Treatment Status	Number of Cases Observed	Complications			Rate per 100
		Pulmonary	Other	Total	
No chemotherapy	209	35	5	40	19
Chemotherapy	382	12	5	17	4

TABLE 2

INCIDENCE OF TUBERCULOUS COMPLICATIONS FOLLOWING PLEURAL EFFUSION AS RELATED TO VARIOUS BACKGROUND FACTORS

	Received Chemotherapy	Did Not Receive Chemotherapy
	per cent	*per cent*
Total rate of complications	4.0	19.0
Race:		
White	3.4	20.0
Non-white	6.4	15.0
Age:		
Less than 40 years	4.4	20.0
40 years and more	4.6	17.0
Type of complication:		
Pulmonary	70.0	88.0
Extrapulmonary	30.0	12.0
Recurrent pleural effusion	31.0	69.0

TABLE 3

THE EFFECT OF CHEMOTHERAPEUTIC REGIMENS UPON THE INCIDENCE OF TUBERCULOUS COMPLICATIONS IN THE TREATMENT OF PLEURAL EFFUSION

Regimen	Number Treated	Number of Complications	Per Cent
Streptomycin only	12	3	25.0
Streptomycin—PAS	250	11	4.4
Isoniazid—streptomycin or isoniazid—PAS	120	3	2.5

group which did not receive chemotherapy. One death occurred in a patient who developed miliary and meningeal tuberculosis twenty-seven months after the onset of the effusion, and the other followed the diagnosis of far advanced pulmonary tuberculosis in a patient twenty-six months after onset of the effusion.

Recurrent pleural effusion was reported in 5 (1 per cent) of the treated group and in 11 (5 per cent) of the untreated series. Of the sixteen recurrences there were seven on the same side as the initial effusion, eight on the contralateral side, and one bilateral recurrence. Adequate data on the bacteriology of the pleural fluid in the recurrent cases was not available. Seven of the eleven recurrences in the untreated group occurred in patients who also had tuberculous complications. One of the five recurrences in the treated group was in a patient who also had a tuberculous complication.

The incidence of complications related to various background factors (table 2) suggests an apparently lower incidence of extrapulmonary complications in the untreated group, a higher rate of complications among the non-whites who received chemotherapy, and a lower incidence of recurrent effusions in the treated group. The incidence of tuberculous complications in those patients less or more than forty years old is equal in both series. However, none of these comparisons is statistically significant.

The incidence of complications related to the antimicrobial agents used was highest among those treated with streptomycin alone (table 3). As noted previously, most of these patients received chemotherapy for less than four months. The lowest incidence is among those who were treated with drug combinations employing isoniazid, and there were also no reported extrapulmonary complications in this group.

The average length of hospitalization for treatment of the effusion among those not receiving chemotherapy who developed tuberculous complications was five months. Forty per cent of this group received hospitalization for two months or less and 43 per cent received hospital treatment for six months or more. Data for the length of hospitalization, with or without chemotherapy, in all cases was not available for this report.

The average length of hospitalization for those receiving chemotherapy who later developed tuberculous complications was six months. Seventy-five per cent of this group developed tuberculous complications while still in the hospital and on chemotherapy. Hospitalization was counted for the period prior to the onset of the complication and more than half the complications occurred within the

TABLE 4

TUBERCULOUS LESIONS AND RECURRENT EFFUSIONS FOLLOWING PLEURAL EFFUSION AS RELATED TO FLUID AND SPUTUM BACTERIOLOGIC FINDINGS

Bacteriology	Patients Receiving Chemotherapy				Patients Not Receiving Chemotherapy			
			Relapses				Relapses	
	Number	Per Cent	Number	Per Cent	Number	Per Cent	Number	Per Cent
Pleural fluid:								
Total tested	331	100	19	100	166	100	41	100
Positive for tubercle bacilli	67	20	9	47	33	20	5	12
Negative for tubercle bacilli	264	80	10	53	133	80	36	88
Unknown	51	—	3	—	43	—	10	—
Sputum:								
Total tested	371	100	20	100	197	100	47	100
Positive for tubercle bacilli	54	15	2	10	18	9	7	15
Negative for tubercle bacilli	317	85	18	90	179	91	40	85
Unknown	11	—	2	—	12	—	4	—

first six months of hospital treatment. Many of these relapses represent parenchymal lesions noted after subsidence of the effusion and extrapulmonary lesions not apparent or symptomatic at the onset of therapy.

Of those patients who were receiving chemotherapy at the time of the development of a tuberculous complication, approximately two-thirds had had therapy for three months or less prior to the finding of the complication. This is perhaps also explained by the comment in the preceding paragraph.

The frequency of subsequent relapse, including both complications and recurrent pleural effusions as related to pleural fluid and sputum or gastric bacteriology, is shown in table 4. Positive cultures or guinea pig inoculations for tubercle bacilli from the pleural fluid were obtained in 20 per cent of the patients tested in both the treated and untreated groups. However, the majority of relapse in both series occurred in those cases in which the pleural fluid bacteriologic findings had been negative. Roper and Waring (1) reported similar findings in their series. This is a highly significant finding and further substantiates the necessity for a firm diagnosis on clinical grounds, even though confirmatory bacteriologic evidence cannot be obtained. The reluctance of patients and physicians to accept the diagnosis and indicated treatment without bacteriologic confirmation may well have serious consequences.

The incidence of relapse to the four-year point after onset of effusion in each series was estimated by the life-table method. The estimated rate for all tuberculous complications at the end of this period of observation in the treated group was 9 per cent, compared with 25 per cent in the untreated group (figure 1). A similar analysis for the complication of pulmonary tuberculosis alone indicated a rate of 7 per cent and 21 per cent, respectively, for the treated and untreated groups (figure 2). The estimated complication rate for the treated cases did not

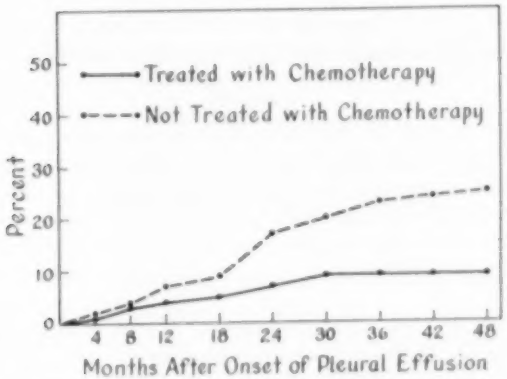

FIG. 1. Estimated rate of development of all tuberculous complications following onset of pleural effusion.

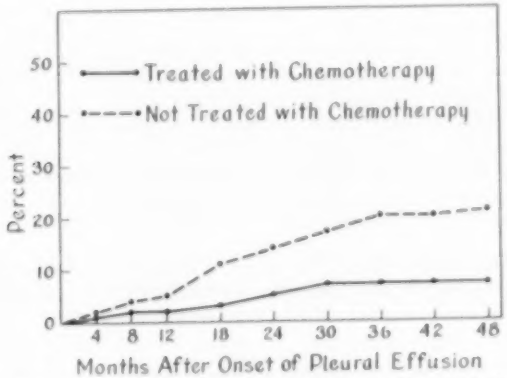

FIG. 2. Estimatesl rate of development of pulmonary tuberculosis following onset of pleural effusion.

increase after the thirty-month point, but did continue to increase for the untreated cases.

The rate of initial bilateral effusion in both the treated and untreated series was the same. However, the rate of complication was 57 per cent among the patients with bilateral effusion in the untreated series and confirms the general clinical impression of the higher morbidity associated with this finding. The rate of complication in the treated group of bilateral effusions was 6 per cent.

It is recognized that certain statistical defects exist in these data, primarily in the nonrandomization of cases, the lack of concurrence in time of the two series, the varying regimens of chemotherapy and duration of therapy, and the possibility of incomplete reporting of cases. The relapse rate of series of patients treated prior to the introduction of the antimicrobial drugs is usually estimated at 35 per cent and has varied from 20 to 65 per cent in various reports for the five years following onset of the pleural effusion. These data and subsequent

reports from the continuing study should offer information of value in estimating the results of chemotherapy in reducing the incidence of tuberculous relapse.

SUMMARY

A comparison is made of the tuberculous complications and recurrence of pleural effusion following the onset of primary tuberculous pleurisy with effusion in a series of patients treated with antimicrobial agents and in those untreated. It is apparent that chemotherapy has sharply reduced the incidence of tuberculous complications following the onset of the tuberculous effusion from 19 per cent in the untreated group to 4 per cent in the treated group followed for four years.

The necessity for a firm clinical diagnosis, despite negative pleural fluid or sputum bacteriologic findings, is substantiated by the high rate of subsequent tuberculous relapse in those patients without proved tuberculous bacteriologic etiology.

SUMARIO

La Terapéutica Antimicrobiana en la Pleuresía Tuberculosa Primaria con Derrame: Su Efecto sobre la Incidencia de Subsecuentes Recidivas Tuberculosas

Trázase aquí una comparación de las complicaciones tuberculosas y la recurrencia de derrame pleural después de la iniciación de pleuresía tuberculosa primaria con derrame en una serie de enfermos tratados con agentes antimicrobianos y otra de sujetos no tratados. Es evidente que la quimioterapia ha reducido agudamente la incidencia de complicaciones tuberculosas consecutivamente a la iniciación del derrame tuberculoso, de 19 por ciento en el grupo no tratado a 4 por ciento en el grupo tratado y mantenido en observación cuatro años.

La necesidad de un diagnóstico clínico seguro, a pesar de una bacteriología negativa en el líquido pleural o el esputo, encuentra apoyo en la alta incidencia de subsecuentes recidivas tuberculosas en estos enfermos sin comprobada etiología bacteriológica tuberculosa.

RESUME

Thérapie antibactérienne dans le traitement de la pleurésie tuberculeuse primaire avec épanchement: Son effet sur l'incidence des rechutes ultérieures de la tuberculose

Les auteurs comparent les complications tuberculeuses et la récurrence de l'épanchement pleural à la suite de l'apparition d'une pleurésie tuberculeuse primaire avec épanchement dans une série de malades traités par des agents antibactériens et chez des malades non traités. Il apparaît que la chimiothérapie a nettement réduit la fréquence des complications tuberculeuses succédant à l'apparition de l'épanchement tuberculeux. L'incidence étant de 19% dans le groupe non traité et de 4% dans le groupe traité suivi pendant quatre années.

La nécessité d'un diagnostic clinique précis, en dépit d'un examen négatif du liquide pleural, est démontrée par le taux élevé des rechutes ultérieures de la tuberculose chez certains malades, alors que l'étiologie bactériologique de la tuberculose n'avait pas eté établie.

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ISONIAZID ALONE IN THE TREATMENT OF PULMONARY TUBERCULOSIS[1]

Two Years' Experience in Previously Untreated Patients

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INTRODUCTION

There are few reports in the literature on the long-term use of isoniazid alone in the treatment of pulmonary tuberculosis. Isoniazid has been reported to be as effective as isoniazid-streptomycin, or isoniazid-para-aminosalicylic acid (PAS) in noncavitary or single cavity lesions, but has been considered to be less satisfactory than those combinations in multiple cavity forms (1, 2). For the last-named reason, isoniazid has not been classed as a maximally effective drug (3, 4). Moreover, there has been a renewed warning against the use of isoniazid alone (5–10). As a result, it has become a common practice to use isoniazid only in multiple drug chemotherapy.

There has also been a common belief, participated in by clinicians as well as surgeons, that cavities still open by the sixth to eighth month of chemotherapy will seldom close on more prolonged chemotherapy (7, 11, 12). Nevertheless, some studies have shown a progressive trend of cavity closure beyond the six- to eight-month point (13, 14), and the results have encouraged (3, 4, 15) a more conservative attitude.

Such controversy affords interest to a more extensive evaluation of isoniazid alone, in particular, in order to establish the length of time its effectiveness is maintained.

A small group of patients has been maintained by the writer on isoniazid therapy, without other measures, for a period of two years. Such long-term single-drug therapy was chosen more because the surgical services were overcrowded and there was a long waiting list than because of any deliberate inclination to keep the patients on a conservative, i.e., nonsurgical, program. The observations made in this series of patients form the basis for the present report.

MATERIAL AND METHODS

The only patients included in the present report were those who had: (*1*) bacteriologic confirmation of diagnosis; (*2*) absence of previous chemotherapy; (*3*) absence of collapse measures after the start of the isoniazid treatment; (*4*) at least nine months of continuous drug treatment.

All of the patients were kept in the hospital (or at home) on bed rest, modified according to the status of the disease.

Therapeutic efficacy was evaluated every three months by roentgenographic changes, based on the customary condensed 3-point scale as read by a "jury" unaware of the regimen. Roentgenographic deterioration included any extension of the disease. Reversal of in-

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fectiousness or "bacteriologic conversion" was considered to have occurred when three cultures taken at least a month apart were negative for tubercle bacilli and no smears had been positive on microscopy. Bacteriologic relapse was considered to have occurred when the status of the sputum changed from negative for tubercle bacilli on smear and culture to positive on smear *or* culture. Cavity was considered to have been closed when a previous cavity was lost to view on body section roentgenograms. Additional data concerning the course of the disease and signs of drug toxicity were obtained from clinical and roentgenographic examinations, routine blood and urine analyses, as well as liver and kidney function tests made at periodic intervals. *In vitro* isoniazid-susceptibility studies were available in only a few cases, and will not be reported here.

Drug therapy: Isoniazid was given orally in three doses a day, at the total daily dosage of 5 or 10 mg. per kg. per day, and the administration was continued for at least nine months.

OBSERVATIONS

Fifty-five patients entered the project from April 21, 1952, to April 24, 1954. Forty-five males were hospitalized, and 6 males and 3 females were cared for at home.

Cases lost to evaluation: Twelve hospitalized patients were lost from observation before the six-month point of evaluation of therapy (table 1). Six left the hospital against medical advice, 4 were discharged and failed to return for follow-up observations, and 2 received a change in therapy. The treatment of one of the last-named 2 patients who had been receiving isoniazid at a dose of 5 mg. per kg. for progressive ulcerocaseous involvement was changed in the second month to isoniazid-streptomycin. This patient died in the seventh month of therapy. The other patient, on transfer to another hospital, was changed to streptomycin-PAS therapy according to the prevalent criteria on that service.

Nine additional patients were lost to observation following the six-month point of evaluation. One patient with moderately advanced and another with far advanced disease left the hospital against medical advice; 4 patients were discharged and could not be traced, and 3 patients were transferred to surgery.

Cases observed for at least a nine-month period on isoniazid alone: Forty-three patients received isoniazid alone for at least nine months; 36, for twelve months;

TABLE 1

PREVIOUSLY UNTREATED CASES OF PULMONARY TUBERCULOSIS DURING ISONIAZID THERAPY (5 TO 10 MG. PER KG. PER DAY)

Cases Lost to Observation

Months After Start of Therapy	0-5	6-11	12-17	18-24
Moderately advanced:				
Unsanctioned discharge	2	1	0	0
Discharged	3	1	0	0
Far advanced:				
Unsanctioned discharge	4	0	0	1
Changed therapy	2	1	2	0
Discharged	1	0	2	1
Total	12	3	4	2

and 29, for fifteen to twenty-one months. Thirty-four patients have completed two years under observation. Twenty-two patients were started on a daily dose of 10 mg. per kg., and 21 on a 5 mg. per kg. dose. In the latter group were 4 of the patients treated earliest who originally received 2 to 3 mg. per kg. with gradual increases to a daily dose of 5 mg. per kg.

Characteristics of cases observed at the beginning of treatment: As may be seen in table 2, the patients were mostly male (40 of 43), young adults (34 of the 43 were less than twenty-nine years of age), with cavitary disease in 39 of the 43. Seventy per cent of the patients had had symptoms for *more* than six months. The pulmonary tuberculosis was far advanced in 26 of the 43 patients, multiple cavities were present in 16, and at least one lobe was destroyed in 8 of the group. In 14 patients, there was a total of 19 instances of extrapulmonary tuberculous complications exclusive of laryngitis or endobronchitis. The complications were: pleurisy with effusion; pericarditis with effusion; peritonitis with ascites; lymph node involvement of the neck, mediastinum, and mesenterium; and bronchopleural fistulas with pneumothorax or empyema.

As the number of patients on each of the two dosage regimens (5 and 10 mg.) was small, the subgroups are inadequate for comparison. As a consequence, it only seems permissible to analyze the results of all of the cases together, with certain subdivisions by stage of disease (National Tuberculosis Association classification).

As may be seen in table 3, substantial roentgenographic improvement was progressive, and was observed at eighteen months in 34 of 36 patients and at twenty-four months in 32 of 34 patients. Bacteriologic "conversion" varied from 77 per cent at twelve months (31 of 40 patients) to 83 per cent at twenty-four months (28 of 34 patients). The values for substantial roentgenographic improve-

TABLE 2

CHARACTERISTICS OF PREVIOUSLY UNTREATED CASES OF PULMONARY TUBERCULOSIS, OBSERVED AT BEGINNING OF TREATMENT

Under Daily Isoniazid Therapy	5 Mg. per Kg.	10 Mg. per Kg.	Total
Number of cases observed	21	22	43 (100)*
Age: 15 to 29 years	15	19	34 (79)
30 and older	6	3	9
Sex: Male	20	20	40 (93)
Female	1	2	3
With symptoms: 0-6 months	4	9	13
More than 6 months	17	13	30 (70)
Moderately advanced	6	11	17
Far advanced	15	11	26 (60)
No cavity	2	2	4
Single cavity	9	14	23 (54)
Multiple cavities	10	6	16 (37)
At least one lobe destroyed	7	1	8 (19)
Extrapulmonary tuberculous complications	7	7	14 (33)

* Percentage distribution in parentheses

TABLE 3

ORIGINAL TREATMENT CASES OF PULMONARY TUBERCULOSIS DURING ISONIAZID THERAPY (5 TO 10 MG. PER KG. PER DAY)

Months After Start of Therapy	6	12	18	24
a) All Cases				
Number of cases observed	43	40	36	34
Substantial roentgenographic improvement	26 (60)*	30 (70)	34 (94)	32 (95)
Bacteriologic conversion	27 (63)	31 (77)	26 (72)	28 (83)
Cavities closed	8 (21)	19 (51)	20 (60)	22 (71)
Roentgenographic deterioration	3 (7)	1	4	3 (9)
Bacteriologic relapse	0	1	4	2 (6)
b) Moderately Advanced				
Number of cases observed	17	15	15	15
Substantial roentgenographic improvement	15 (68)	14 (93)	15 (100)	15 (100)
Bacteriologic conversion	14 (82)	13 (87)	12 (80)	13 (87)
Cavities closed	5 (38)	10 (83)	11 (92)	11 (92)
Roentgenographic deterioration	0	0	1	0
Bacteriologic relapse	0	0	1	0
c) Far Advanced				
Number of cases observed	26	25	21	19
Substantial roentgenographic improvement	11 (42)	16 (64)	19 (91)	17 (90)
Bacteriologic conversion	13 (50)	18 (72)	14 (75)	15 (79)
Cavities closed	3 (12)	9 (42)	9 (40)	11 (61)
Roentgenographic deterioration	3 (12)	1	3	3 (16)
Bacteriologic relapse	0	1	3	2 (11)

* Percentage distribution in parentheses

ment and bacteriologic conversion in the far advanced cases showed no great differences from the values for the group as a whole. The percentage distribution of these results was not significantly distorted by the 9 cases lost during observation, as 6 had already shown substantial roentgenographic improvement with bacteriologic "conversion." The rate of cavity closure was also progressive, varying from 8 of the 39 original cavitary cases at six months to 19 at twelve months, and 22 with cavity closure at the end of the second year. To express these results differently: Of 25 patients whose cavities all closed, the closure occurred during the first semester in 8 patients, during the second semester in 12 patients, and in 5 patients the cavities closed slowly and finally disappeared only during the second year. In 15 of the 23 patients with single cavities (65 per cent), and in 5 of the 16 with multiple cavities (31 per cent), closure of all cavities was observed within twelve months of the start of treatment.

Three cases seem representative of the average among the multiple-cavity cases and are presented in detail (*Cases 1*, *2*, and *3*, Plates I, II, and III).

Progression of disease during or after isoniazid therapy: Nine instances of

deterioration occurred in 7 patients. In only one case, a cavity enlargement, did the deterioration seem to begin while the patient continued to receive chemotherapy. In all of the other cases, the relapse occurred between six to twelve months after *cessation* of the isoniazid therapy. In one case the previously improved infiltrates flared up and, in 3 cases, a small cavity reopened. In 4 additional instances the sputum "reverted" to positive. In no instance did extension of infiltration occur, nor did totally new areas of disease develop while the patients were continuing to receive chemotherapy. In 2 cases a small cavity closed again; and, in 2, bacteriologic relapse "converted" again following reinstitution of isoniazid therapy.

Extrapulmonary lesions: All of the 19 instances of extrapulmonary tuberculous complications present at the beginning of treatment in the 14 patients responded satisfactorily to isoniazid alone, as judged by present clinical standards. One case seems of particular interest (*Case 4*, Plate IV).

Isoniazid toxicity: Only one of the 43 patients exhibited, in the ninth month of treatment, signs of clinical significance attributable to drug intolerance. The symptoms were those of peripheral neuritis, and the drug was discontinued. Attempts to resume isoniazid in the twelfth and seventeenth months of observation brought up recurrence and extension of the neuritis. The gastric cultures had remained negative for tubercle bacilli since the sixth month of therapy and all cavities had disappeared by the ninth month of treatment.

DISCUSSION

Forty-three previously untreated patients with advanced pulmonary tuberculosis received isoniazid orally in a daily dose of 5 and 10 mg. per kg. for a period of at least nine months. In 36 cases the drug was administered for twelve months; and in 29, for fifteen to twenty-one months. Thirty-four of the 43 patients completed a two-year period of observation. During the second year of follow-up, substantial roentgenographic improvement increased from 70 to 95 per cent (32 of 34 patients at twenty-four months), bacteriologic conversion was maintained, with little change, at approximately 80 per cent, and cavity closure increased from 50 to 70 per cent. Deterioration during this period of time was approximately 10 per cent and, with one exception, occurred only after the cessation of the isoniazid therapy.

Such a high incidence of substantial roentgenographic improvement—even in the far advanced cases—must not be looked upon by itself as synonymous with complete therapeutic success. When pulmonary tuberculosis is treated for the first time, it usually contains a great deal of pathology of regressive character. It is only logical, therefore, to expect considerable clearing among most previously untreated cases without meaning, for that reason, that the drug regimen used was completely effective. That "substantial improvement" is not a very reliable index to evaluate long-term chemotherapy has already been observed by D'Esopo (16), McDermott and associates (17), and Tucker (2).

The high level of reversal of infectiousness and of cavity closure seems significant in the type of cases in the present series (table 2). In 26 of the 43 patients

the pulmonary tuberculosis was far advanced; in 16, multiple cavities were present; at least one lobe was destroyed in 8 patients; and extrapulmonary tuberculous complications were present in 14 of the 43 patients.

Analysis of the bacteriologic results in concurrently randomized cases under isoniazid alone, or combined with streptomycin or PAS, shows only slight superiority of the combined over the single isoniazid regimen (18–20), except for the Medical Research Council studies. In these studies, streptomycin daily plus isoniazid was considered to be significantly superior at the three-month evaluation point (21).

The Cornell group of investigators, on the basis of their study of the course of pulmonary tuberculosis (22), their previous experience in miliary and meningeal tuberculosis (23), and an extensive review of the literature, concluded that in terms of long-term continued effectiveness isoniazid alone was comparable with the other chemotherapies. Tucker (2), on revising the data from the earliest isoniazid studies in the Veterans Administration hospitals, also reached the conclusion that isoniazid alone was comparable with isoniazid-streptomycin (latter drug, twice weekly) and streptomycin-PAS in noncavitary and single cavity cases. Aside from the fact that isoniazid has usually been administered alone only for short periods of time, the drug has often been used in doses of 150 to 200 mg. (2, 18–21), which may be subtherapeutic in many cases. It has been found that the 3 mg. dose equals the 10 mg. dose in therapeutic effectiveness on short-term evaluation (24). However, the more potent antimicrobial effect of the higher over the lower doses of isoniazid alone has been demonstrated since the first isoniazid trials *in vivo* (25, 26). More recently, in treating naturally acquired tuberculosis in the rhesus monkey, Schmidt, Hoffmann, and Jolly (27) found that the incidence of tissue culture positive on the 20 and 80 mg. doses was 21 per cent and 17 per cent, respectively, while on the 5 mg. dose, it was 71 per cent. These facts would indicate that the clinical testing of isoniazid has not been always performed on a fully therapeutic dosage, and it would be unjustifiable to conclude from such limited trials that isoniazid alone is necessarily inferior to isoniazid in multiple-drug regimens.

The rate of cavity closure at twelve months in the present series was similar to the results obtained under isoniazid-PAS or isoniazid-streptomycin for all types of cases, and even for multiple-cavity cases (13), although it was inferior to the results obtained by others within the limits of one year (28, 29). Naturally, any influence on the course of the disease through therapy must first be related to the background factors of the cases under study and not only to the type of therapy used.

It has been a common finding that most of the cavities which are going to close in twelve or more months of chemotherapy will have closed within six months (7, 11, 12). More recently, however, the multiple-drug regimens afford a progressive trend of cavity closure which doubles from the fourth to the eighth month, and triples by the twelfth month of treatment (13). Brouet and Marche (14) find a double increase in cavity closure, from the sixth to the eighteenth month or more, under streptomycin, PAS, and isoniazid given in various combinations.

This new experience would indicate that the six- to eight-month period may not be the optimal time period to estimate the full therapeutic effect of a drug regimen, as measured by cavity closure. In the present report the percentage of cavity closure tripled from the sixth to the twelfth month, and there was a slight increase above that value during the second year. Consequently, the therapeutic efficacy of isoniazid alone, as measured by the behavior of cavities, compares favorably with the therapeutic efficacy of isoniazid in association with other drugs.

Unfavorable roentgenographic changes or bacteriologic relapse in the present study were within the limits observed by others for the multiple-drug regimens (18–21). Such deterioration in the present series occurred chiefly in patients whose isoniazid therapy was discontinued around the ninth month of treatment, suggesting that this interval may represent too short a period of treatment.

On clinical grounds only, there were no signs which could be attributed to isoniazid resistance during this trial. There is no doubt that some adaptive mechanism, or resurgence of mycobacteria to its full pathogenic phase, actually appears *in vivo*, while the patient is receiving isoniazid treatment. But it did not become apparent during nine to twenty-one months of isoniazid intake in the present series. Late unfavorable roentgenographic changes and bacteriologic relapse were reversed or restrained following readministration of isoniazid, suggesting again that these early relapses were of a benign character. Side-reactions to isoniazid at 5 to 10 mg. occurred in only one of 43 cases.

It was established in the Public Health Service reports (24) that toxicity to isoniazid at the dose of 10 mg. plus streptomycin, which necessitated a change in chemotherapy, was 11 to 14 per cent, and toxicity to isoniazid at 10 mg. plus PAS was 18 to 23 per cent, during twenty and thirty-two weeks of treatment, respectively. It has not been determined, to the writer's knowledge, whether isoniazid, if used alone, at the same dose is equally toxic.

On the other hand, the main objection to the use of multiple chemotherapy is the potential risk of developing multiple-drug resistance. The Public Health Service (30) has reported that "the regimen (streptomycin-isoniazid) which offers the greatest probability of 'negative' sputum, provides also the near certainty of bacilli resistant to both streptomycin and isoniazid if the sputum has not become free of tubercle bacilli." Mitchell also established (11) that "prior PAS therapy and *in vitro* PAS resistance have just as adverse an influence on results with prolonged streptomycin-PAS retreatment as prior streptomycin therapy and *in vitro* streptomycin resistance." Moreover, Jenney and Landis (31) conclude that development of resistance to isoniazid is not significantly retarded by the use of either streptomycin or PAS.

SUMMARY

Forty-three cases of advanced pulmonary tuberculosis were treated for the first time for at least nine months with isoniazid at the daily doses of 5 and 10 mg. per kg. In 36 cases isoniazid administration was prolonged for twelve months, and in 29 for fifteen to twenty-one months. In 34 cases after two years of obser-

vation, 83 per cent had reversal of infectiousness and in 71 per cent all cavities were closed. Analysis of these results offers clinical evidence to suggest that the therapeutic efficacy of the single-drug isoniazid regimen is not dissimilar to the therapeutic efficacy of isoniazid-streptomycin or isoniazid-PAS, and that the higher doses of isoniazid must be more extensively investigated.

SUMARIO

La Isoniacida en el Tratamiento de la Tuberculosis Pulmonar. Dos Años de Experiencia en Enfermos Tratados Inicialmente

Cuarenta y tres casos de tuberculosis pulmonar avanzada fueron tratados por primera vez a lo menos nueve meses con isoniacida a dosis diarias de 5 y 10 mg. por kg. de peso. En 36 casos, la administración de isoniacida se prolongó hasta doce meses y en 29 de quince a vientiún meses. En 34 casos mantenidos en observación dos años, 83 por ciento mostraron viraje de la infecciosidad y en 71 por ciento cierre todas las cavernas. El análisis de estos resultados ofrece evidencia clínica suggestiva de que la eficacia terapéutica del régimen de isoniacida sola no es disimil a la eficacia terapéutica de la isoniacida-estreptomicina o de la isoniacida-PAS, y de que deben investigarse más extensamente las dosis más altas de isoniacida.

RESUME

L'isoniazide dans le traitement de la tuberculose pulmonaire: Deux années d'observation de malades soumis au traitement initial

Quarante-trois cas de tuberculose pulmonaire avancée furent traités pour la première fois pendant au moins neuf mois avec l'isoniazide à la dose de 5 et de 10 mg/kg par jour. Dans 36 cas l'administration de l'isoniazide fut prolongée pendant douze mois et dans 29 cas pendant quinze à vingt et un mois. Dans 34 cas, au bout de deux années d'observation, on a observé la négativité des crachats chez 83% d'entre eux et l'oblitération de toutes les cavernes dans 71% des cas. L'analyse de ces résultats offre des preuves cliniques suggérant que l'efficacité thérapeutique du traitement par l'isoniazide seule ne diffère pas de l'efficacité thérapeutique de l'association isoniazide-streptomycine ou isoniazide-PAS, et qu'il y a lieu de procéder à des recherches extensives sur l'emploi de l'isoniazide, á doses élevées.

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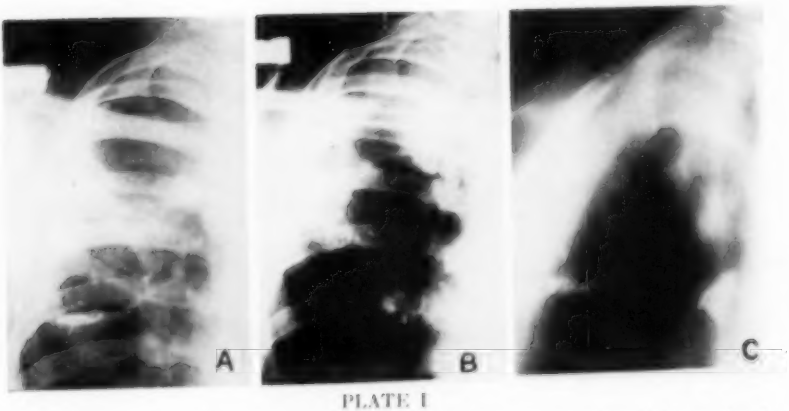

PLATE I

Case 1. P. R., an 18-year-old boy with far advanced pulmonary tuberculosis, active for five months, had huge cavities in the right lung (*A*, dated April 12, 1954) and remittent fever. He was coughing up 70 to 100 ml. of mucopurulent sputum daily. His body weight was 75 per cent of normal, the hemoglobin value was 7 gm. per 100 ml. of blood, and there was a leukocytosis of 18,000 per cu. mm. The patient was treated with isoniazid, 10 mg. per kg. per day for nine months, starting on April 24, 1954. He also received ferrum sulfate, parenteral penicillin, and a blood transfusion of 300 ml. Gastric cultures were first negative for tubercle bacilli after eight months of therapy and the cavities diminished remarkably (*B*, obtained January 12, 1955). Nine months after the cessation of isoniazid therapy, tubercle bacilli reappeared in the sputum and the patient became febrile. A second course of isoniazid was started, 10 mg. per kg., twenty months after the start of the first chemotherapy. The fever disappeared again, but tubercle bacilli continued to be present in the sputum and a cavity failed to close (*C*, obtained February 15, 1956).

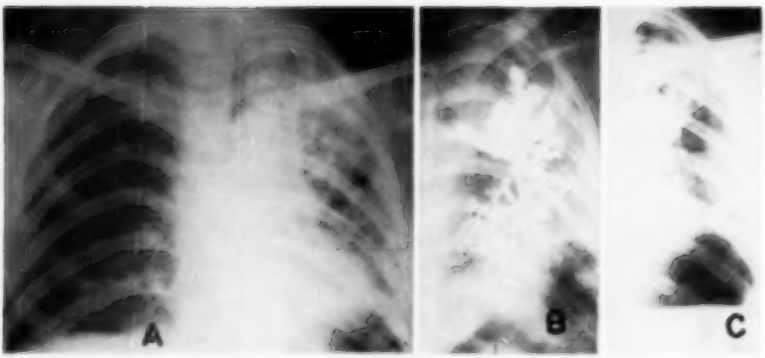

PLATE II

Case 2. The patient, B. G., was a 29-year-old man with almost the entire left upper lobe destroyed by tuberculosis, as demonstrated by a chest roentgenogram, dated July 6, 1953 (*A*), and a bronchogram, dated January 23, 1954 (*B*). The patient had had symptoms for the previous three years, with hemoptysis. On admission he also had two draining sinuses from enlarged lymph nodes in the neck. He was treated with isoniazid, 5 mg. per kg. per day, starting on August 15, 1953. Gastric cultures "converted" at the sixth month of treatment. The patient left the hospital against medical advice in the ninth month of treatment and discontinued the drug. He worked as a laborer and returned to the hospital sixteen months after the start of chemotherapy with hemoptysis and tubercle bacilli in the sputum. He had recently suffered a chest trauma (*C*, obtained November 9, 1954). The patient received a second course of isoniazid, 5 mg. per kg. per day, and the gastric cultures for tubercle bacilli again became negative two months after the start of the second course of chemotherapy.

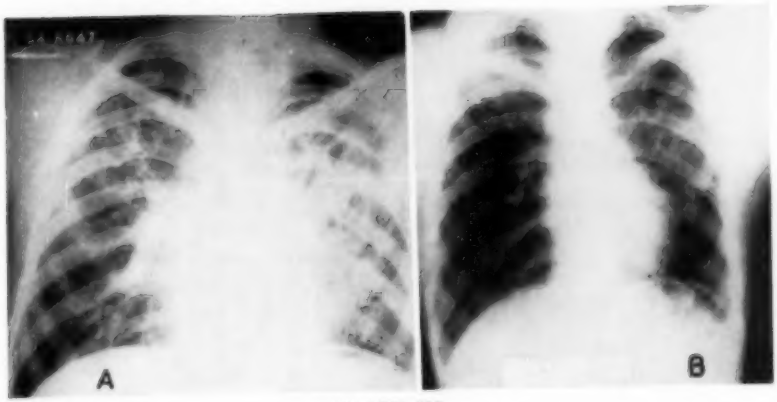

PLATE III

Case 3. L. P., an 18-year-old boy, had tuberculosis with multiple cavities in the left lung (*A*, obtained March 3, 1954) which had been active for one year. The patient received isoniazid, 10 mg. per kg. per day, starting on April 4, 1954. At the end of nine months of treatment the drug was discontinued for three months and was resumed for the following twelve months. Gastric cultures for tubercle bacilli became negative in the seventh month of therapy and all cavities were closed during the fourth six-month period of treatment (*B*, dated May 4, 1956).

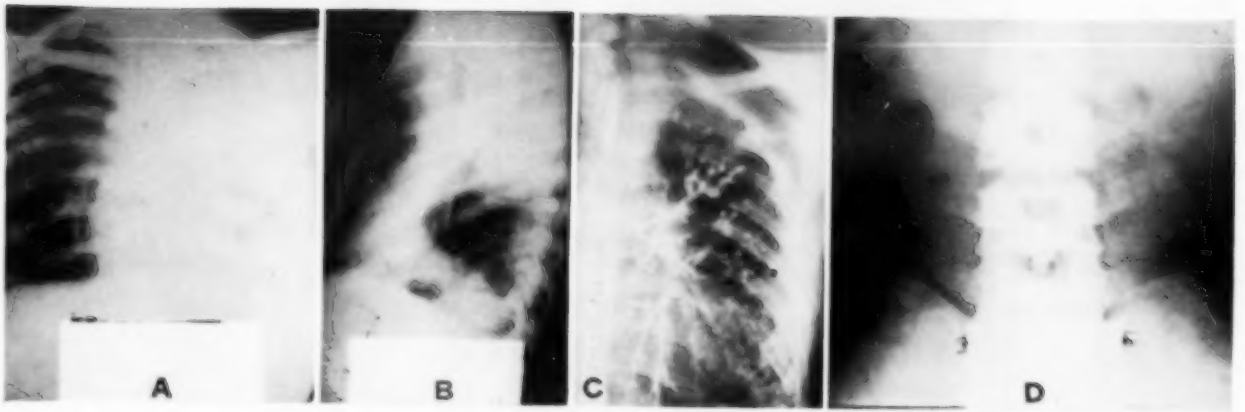

PLATE IV

Case 4. R. T., a 16-year-old boy, suffered from pneumonic cavitary tuberculosis of the left upper lobe (*A*, dated July 2, 1953), which had been active for ten months. He also had enlarged lymph nodes of the neck (9 by 5 by 4 cm. bilaterally, and 3 cm. large in the axillae and abdomen), left pleurisy with effusion, which cleared promptly (*B*, dated September 16, 1953), and a peritonitis with ascites. The patient was admitted to the hospital in a critical condition. His body weight was 68 per cent of normal and he had high fever, diarrhea, hematuria, and anemia. The hemoglobin value was 9.5 gm. per 100 ml. of blood. The patient received isoniazid, 10 mg. per kg. per day, starting on July 6, 1953, for a period of twelve months. The drug was discontinued for a period of three months and was re-started in a second course for the rest of the observation period. Gastric cultures became negative for tubercle bacilli and the cavity closed during the seventeenth month of observation. Sacular bronchiectasis persisted in the apico-posterior segment (*C*, dated August 10, 1955), and the lymph nodes of the neck and abdomen calcified (*C* and *D*, dated August 25, 1955).

STUDIES ON PREVENTION OF EXPERIMENTAL TUBERCULOSIS WITH ISONIAZID[1]

II. Effects of Different Dosage Regimens

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INTRODUCTION

The general features and methods of a laboratory research program to see whether isoniazid could be used to prevent tuberculosis in guinea pigs have been described in a previous report (1). Results of the first in a continuing series of projects indicated that guinea pigs can be protected against a massive inoculation of virulent tubercle bacilli by a ten-week course of isoniazid in daily doses as low as 5 mg. per kg. of body weight. Evidence of protection was shown by survival and growth curves similar to a comparable group of normal untreated, uninfected animals during the ten-week period of treatment and an additional sixteen weeks of observation after the drug had been discontinued. A secondary but important finding was that animals given a second massive inoculation shortly after isoniazid had been discontinued had some resistance against later reinfection.

The present paper outlines the results of three subsequent projects undertaken to probe further into the matter of dosage regimens—different amounts of isoniazid administered daily or intermittently for various periods of time.

PLAN OF INVESTIGATION

A description of the principles and procedures is given in earlier papers (1, 2), in which are discussed the basic elements in the design of the studies, the preparation of detailed protocols before each project is started, and the methods used to avoid observer bias and ensure comparability among the various groups of animals.

Random-bred guinea pigs have been chosen for these studies on the ground that they might represent better than any special strain the wide range of variation found in human populations. Moreover, although efforts are made to eliminate diseased animals during a three-week quarantine period before a study is started, it has not been considered advisable to use only highly selected healthy animals or to attempt to increase their natural resistance through special diets. The reason for this is, again, that results obtained from large numbers of "run of the mill" populations of animals would most nearly parallel those that might be expected in human populations, including underprivileged groups in some parts of the world.

In the four projects described in this and an earlier report, a massive inoculation of virulent tubercle bacilli has deliberately been used to provide stringent

[1] From the Tuberculosis Program, Division of Special Health Services, Public Health Service, Washington, D. C.

conditions for the test of isoniazid. If isoniazid can successfully prevent the otherwise rapidly fatal course of disease resulting from an overwhelming inoculation, it could also be expected to control as effectively a smaller infecting dose. Although little is known about the size of the infecting dose under natural conditions in human beings, it is often referred to as massive and repeated, particularly in infants and young children. Moreover, multiplication of bacilli *in vivo* may well convert a small initial inoculum into a massive infection within a short period of time. In this connection, however, it may be mentioned that graduated series of inocula, ranging from a very large to a very small number of virulent tubercle bacilli, are being used in other studies now in progress.

At the outset of these studies it became apparent that little information is available on mortality, growth, water consumption, et cetera for large populations of random-bred guinea pigs observed over long periods of time. The literature contains extensive material on many animal species in which large economic interests are concerned, but there has been no similar motivation for making carefully documented observations on random-bred guinea pigs. The experience of suppliers is generally confined to young animals and breeding stock.

For the present program, therefore, it has been necessary to make detailed observations, particularly on the basic patterns of water consumption, growth, and mortality of normal guinea pigs. The consistency of certain patterns observed in large groups of animals received every few months during the past several years has provided a fairly substantial body of data for predicting what may be expected of normal random-bred guinea pigs in this laboratory. A detailed report on some of these observations is now in progress.

The administration of isoniazid in the drinking water was discussed in the preceding report (1). Briefly, the animals were given a standard, presumably adequate, diet of dry pellets fortified with vitamin C to force them to get their fluids by drinking water. Observations show that on that diet the animals drink, on the average, approximately 10 per cent of their body weight of water per day. The relation between body weight and water intake thus permits regulation of the per kilogram dosage by varying the concentration of isoniazid in the drinking water. For example, an isoniazid concentration of 0.01 mg. per ml. in the drinking water is assumed to give an average daily dose of approximately 1 mg. per kg. of body weight; a concentration of 0.20 mg. per ml., to give 20 mg. per kg., et cetera. For simplicity, dosage will be expressed hereafter as milligram per kilogram of body weight, based on the concentration of isoniazid put into the drinking water and the assumption that the animals drank 10 per cent of their body weight per day.

OBSERVATIONS

Variations in Dose and Frequency of Isoniazid Administration (Project *C*)

The purpose of the project designated as *C* was to assay the relative effectiveness of different regimens, ranging from a total of 5 mg. to 35 mg. of isoniazid per kg. per week, given daily or intermittently, for either ten weeks or twenty-two weeks.

TABLE 1

PROJECT C: OUTLINE OF EXPERIMENTAL GROUPS, PROCEDURES, AND NUMBER OF GUINEA PIGS SURVIVING OR SACRIFICED AT SPECIFIED WEEKS AFTER INOCULATION OF VIRULENT TUBERCLE BACILLI (OR SALINE)

Group	Isoniazid*		Challenge (C) or Saline (S)	Number of Animals at Specified Weeks							
				Surviving							Sacrificed†
				0	4	8	12	16	20	22	0–3
	mg/kg	*days/wk*									
Normal	—	—	S	120	77	69	64	60	‡		24
Control	—	—	C	59	38	24	10	4	1	1	1
1	2	7	C	60	47	36	30	25	22	22	1
2	3	3	C	60	35	22	18	17	14	14	1
3	3	7	C	60	47	40	37	35	32	31	3
4	4	3	C	58	43	38	32	30	28	27	1
5	4	7	C	60	50	44	44	42	40	40	2
6	5	1	C	59	48	41	33	30	24	23	3
7	5	3	C	60	47	41	38	38	37	36	2
8	5	7	C	58	46	38	36	33	30	30	2
9	10	3	C	60	47	40	36	36	33	32	1

* For *Groups 1* and *2*, given for 22 weeks; for *Groups 3* to *9*, given for 10 weeks to half, for 22 weeks to other half of each group, starting 48 hours before challenge

† For special examination to determine cause of intercurrent epidemic disease

‡ 57 animals withdrawn at 19 weeks for another project

The project was started with 720 random-bred male and female guinea pigs having an average weight of approximately 500 gm. The animals were allocated by a randomization procedure to one group of 120 and ten groups of 60 each. Certain pertinent facts about the project are given in table 1.

The group of 120 animals, referred to as the normal group, provided a baseline for assessing the effects of the experimental procedures applied to the various other groups. The normal group was not given isoniazid and, instead of an inoculation of virulent tubercle bacilli, was given an intraperitoneal injection of 0.5 ml. of normal saline solution. Another group, the control group, was inoculated with virulent tubercle bacilli but was not given isoniazid. The animals in the nine other groups were started on different dosage regimens of isoniazid and were then inoculated, as indicated in table 1. The drug was started forty-eight hours before the inoculation. For *Groups 1* and *2*, isoniazid was given for twenty-two weeks; half the animals in each of *Groups 3* through *9* received the drug for ten weeks, the remaining half for twenty-two weeks. For the three-day-a-week regimens, isoniazid was put in the drinking water on Mondays, Tuesdays, and Fridays.

The inoculation of virulent tubercle bacilli was given intraperitoneally in 0.5 ml. of a diluted liquid Tween®-albumin suspension of H37Rv. As determined by plate counts, the suspension used in this project contained approximately 7.5×10^5 viable bacillary units per 0.5 ml. The project was started on March 10, 1955, and was terminated at the end of twenty-two weeks.

Mortality: The percentage of animals which survived at the end of each week after inoculation is shown graphically in figure 1. Separate curves are shown for the control animals (inoculated but not given isoniazid), the normal animals (not inoculated and not given isoniazid), and for four of the nine groups inoculated and given isoniazid. Curves for the five remaining groups were almost

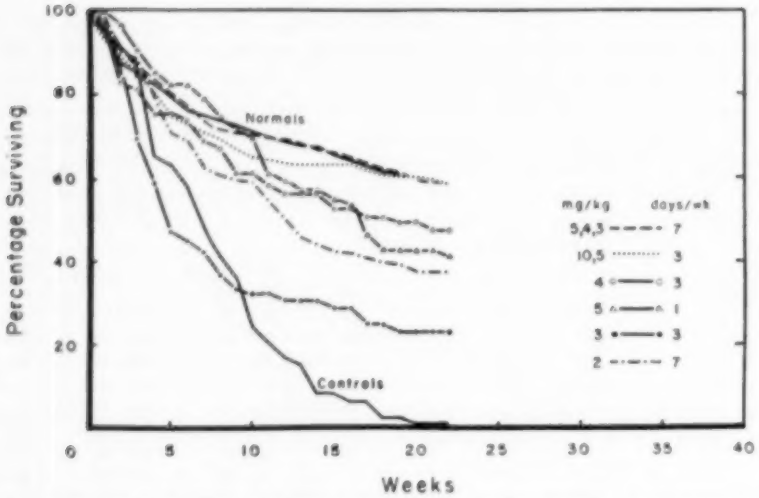

FIG. 1. *Project C:* percentage of guinea pigs alive at weekly intervals after inoculation of virulent tubercle bacilli (or saline), according to dosage of isoniazid regimen (percentages adjusted for animals sacrificed).

indistinguishable and have been combined into two curves: one obtained by combining the groups that received 5, 4, or 3 mg. per kg. daily; the other by combining those that received 10 or 5 mg. per kg. three days a week. Results for animals given isoniazid for ten weeks or for twenty-two weeks are combined in figure 1 (but shown separately in figure 2). Adjustments have been made throughout for animals sacrificed during the course of the experiment.

The rather high mortality for all groups, including the normal animals, during the early weeks was caused by an intercurrent nonpulmonary disease that was highly prevalent for a short time and then gradually disappeared. As clinical signs of the disease seemed to be equally prevalent in all groups, differences in survival among the groups are ascribed to the effects of the different dosage regimens of isoniazid.

Animals in the control group died rapidly: less than 50 per cent were still living seven weeks after the inoculation and less than 10 per cent by the end of the fourteenth week. Mortality in the group given 3 mg. of isoniazid per kg. three days a week was as great as in the control group for the first nine weeks, but relatively few animals died during the remainder of the twenty-two-week period. Mortality in the groups given 2 mg. of isoniazid per kg. daily, 5 mg. per kg. one day a week, and 4 mg. per kg. three days a week was less than in the control group but greater than in the normal group. Finally, the same proportion of the normal group and of the animals receiving 5, 4, or 3 mg. per kg. daily, or 10 or 5 mg. per kg. three days a week, was surviving at the end of twenty-two weeks.

The effect on mortality of discontinuing isoniazid after ten weeks is shown in

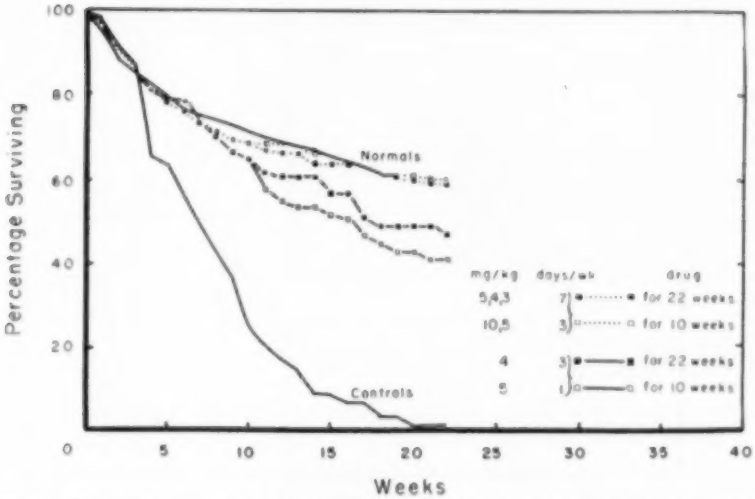

FIG. 2. *Project C:* percentage of guinea pigs alive at weekly intervals after inoculation of virulent tubercle bacilli (or saline), according to dosage and duration of isoniazid regimen (percentages adjusted for animals sacrificed).

figure 2, in which results for various regimens have been combined as indicated. Animals given 4 mg. per kg. three days a week or 5 mg. per kg. one day a week died more rapidly when the isoniazid was discontinued after ten weeks than when it was continued for twenty-two weeks. In contrast, animals given 5, 4, or 3 mg. per kg. daily or 10 or 5 mg. per kg. three days a week survived as well whether the isoniazid was given for ten or for twenty-two weeks.

Growth in body weight: Results of weekly measurements of body weight are shown in figure 3, in which each curve is based on the mean weight of the surviving animals in each group or combination of groups (*cf.* figure 1). At the time of the inoculation, the mean body weight of the animals in each group was close to 500 gm. During the next two weeks, animals in all groups lost weight, presumably owing to the intercurrent disease prevalent at that time. The control animals continued to lose during the following few weeks when many of them were dying of tuberculosis, and a mean weight of less than 540 gm. was observed in the twelfth week when only 10 animals were still alive. In contrast, after the second week, the normal animals gained rapidly and steadily to reach a mean weight of 825 gm. at the eighteenth week, just before the group was withdrawn from the study. The groups receiving 5, 4, or 3 mg. per kg. daily or 10 or 5 mg. per kg. three days a week, although lagging slightly behind the normal animals during the early weeks, gained like the normal animals during the rest of the observation period. Weight of the other groups ranged between that of the normal and control groups during the first six weeks, then increased rapidly and tended to approximate that of the normal group by the end of the study.

Tuberculin sensitivity: Intradermal tuberculin tests with 0.005 mg. of PPD-S

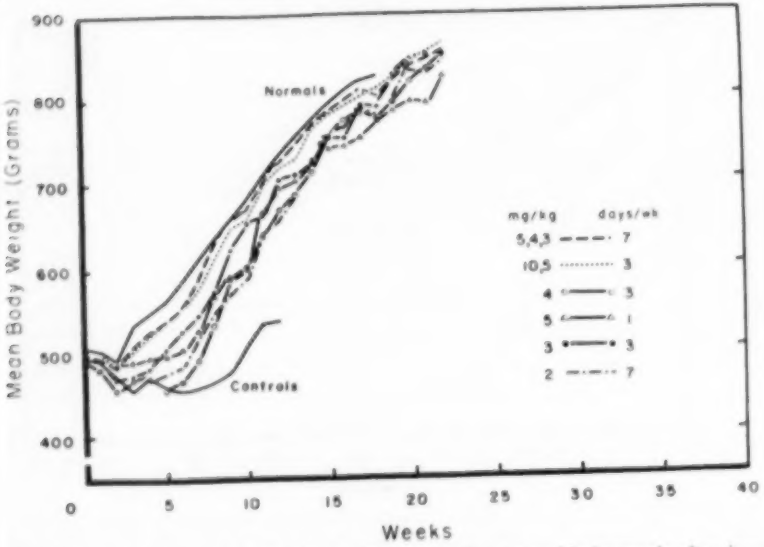

FIG. 3. *Project C*: mean body weight of guinea pigs alive at weekly intervals after inoculation of virulent tubercle bacilli (or saline), according to dosage of isoniazid regimen.

in 0.1 ml. were given to all surviving animals at four, eight, twelve, and sixteen weeks.

The technique of testing and reading the reactions was discussed in detail in an earlier report (3). Briefly, the tests are given on specified sites on the abdomen, the same site being used for all animals at a single testing session. Reactions are read at forty-eight hours by measuring the transverse diameter of induration with a millimeter ruler. For both testing and reading, animals are taken in a random order from all experimental groups, control and normal animals intermixed with the various other groups, and the tester and reader are not allowed to know the group to which any animal belongs. In this way, bias resulting from prejudgment is eliminated and observational errors are randomly distributed over all experimental groups.

The kind of results generally obtained in testing a group of infected animals is illustrated in figure 4. Two frequency distributions are shown for sizes of reactions obtained in the present project, one for the testing at the eighth week of the groups receiving 3 mg. per kg. three days a week and 2 mg. per kg. seven days a week, and the other for the testing at the sixteenth week of the groups receiving 5, 4, or 3 mg. per kg. daily. In both distributions the reactions are fairly symmetrically distributed around the mean, which is 17.9 mm. for one group and 10.8 mm. for the other. These examples illustrate that the mean size of the reactions is an efficient index of the degree of tuberculin sensitivity exhibited by the animals in each group.

The mean sizes of the tuberculin reactions of the various groups of animals at four different periods are given in figure 5. Results for the normal animals

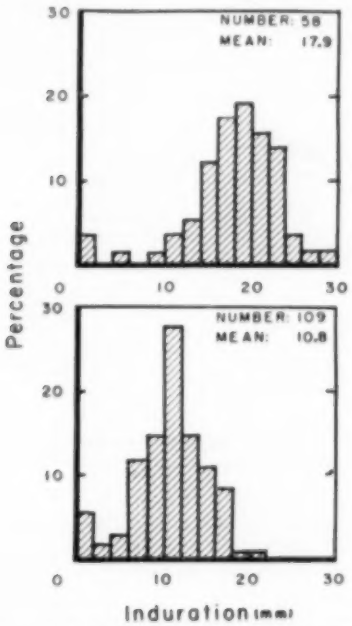

FIG. 4. *Project C*: frequency distributions of size of intradermal reactions to 0.005 mg. of PPD-S for two groups of guinea pigs after receiving isoniazid and an inoculation of virulent tubercle bacilli.

are not included because, except for a few that gave very small reactions, they remained nonreactors to tuberculin throughout the experiment. At the first testing session four weeks after the inoculation, most of the animals in all other groups had become sensitive to 0.005 mg. of PPD. The mean sizes of the reactions were fairly similar for each group, but definite differences can be discerned that tend to be maintained at subsequent periods. For example, the groups which received the most effective regimens of isoniazid (5, 4, or 3 mg. per kg. daily and 10 or 5 mg. per kg. three days a week) had the lowest degrees of tuberculin sensitivity throughout the course of the experiment; those which received less effective regimens tended to have slightly larger reactions. The control animals, except for the few animals that survived to the twelfth week, developed approximately the same degree of sensitivity as the animals on the less effective isoniazid regimens. Although the details are not shown, the mean sizes of the tuberculin reactions were somewhat smaller at the end of the experiment for animals given the drug for twenty-two than for ten weeks.

Changes in the degree of tuberculin sensitivity from one testing session to another cannot be interpreted without reservations: although every effort is made to keep the testing uniform throughout the course of an experiment, unknown variations in the observer's technique from time to time, the effect of

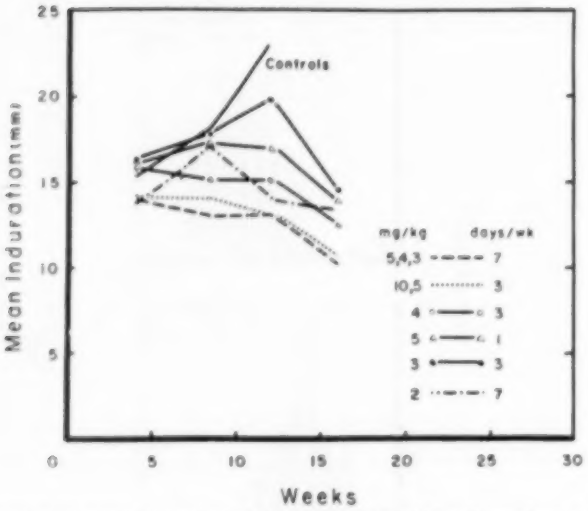

FIG. 5. *Project C:* mean diameter of induration of intradermal reactions to 0.005 mg. of PPD-S for guinea pigs alive at specified intervals after inoculation of virulent tubercle bacilli, according to dosage of isoniazid regimen.

systematically rotating the testing site on the animal's abdomen, as well as other factors, may influence the results obtained at different testing sessions. On the other hand, differences among the groups at any one testing session almost certainly represent real differences. Thus, the results shown in figure 5 indicate that under the conditions of the present project the guinea pigs that received isoniazid regimens adequate to prevent mortality from tuberculosis developed slightly lower levels of tuberculin sensitivity than the unprotected control animals and the groups which received inadequate doses of the drug.

Gross tuberculous pathology: Post-mortem examinations made on animals that died during the course of the experiment have been limited primarily to observations on gross pathologic evidence of tuberculosis. The animal quarters are inspected twice a day; the dead are removed and an autopsy is performed as soon as practicable. Efforts are made to examine all animals that die, but because of inevitable delays some become unsuitable even for gross examination. To ensure objective observations, the observer is not allowed to know the group to which any animal belonged. The autopsy examination is only partial: the abdomen and thorax are opened; the liver, spleen, omentum, and lungs are removed, weighed, and examined grossly for signs of tuberculosis; the abdominal and thoracic cavities and the remaining organs are then inspected. Finally, on the basis of the findings, each animal is classified into one of six categories: negative for tuberculosis, or tuberculosis graded according to severity of disease from plus-minus to 4-plus.

During the twenty-two-week course of the project, a total of 369 animals

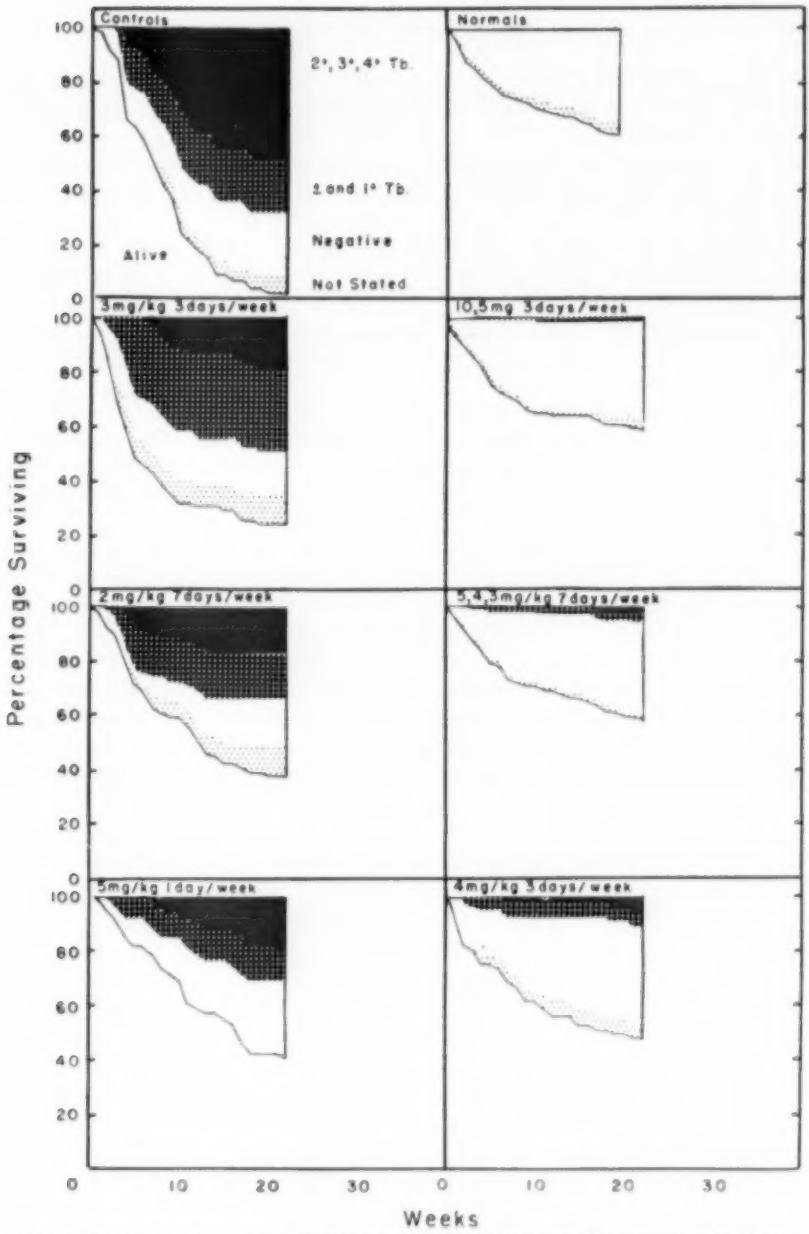

FIG. 6. *Project C:* percentage of guinea pigs alive or dead at weekly intervals after inoculation of virulent tubercle bacilli (or saline), according to dosage of isoniazid regimen; the dead classified according to gross evidence of tuberculosis at autopsy (percentages adjusted to exclude animals sacrificed).

died and all but 31 of them were examined post mortem. Further details are given in figure 6, in which each section represents one group (or combination of groups) of animals and shows, in each week, the percentage alive and dead; and, for those that died, their distribution according to gross pathologic findings. For summary purposes, the plus-minus and 1-plus categories are combined, and the 2-, 3-, and 4-plus categories are also combined.

As shown in the upper left-hand section of figure 6, a high proportion of the control animals died with signs of extensive tuberculosis. Of the 59 animals in that group, only one was still alive when the project was terminated and one had been sacrificed. Of the 57 that died, 28 were classified as having 2-plus disease or more, 11 as plus-minus or 1-plus, 14 as negative for tuberculosis, and 4 were not examined.

The results for the normal animals shown in the upper right-hand section of the figure contrast sharply with those for the control animals. When the normal animals were withdrawn for another project at the nineteenth week, more than 60 per cent were still alive and, of those that had died and were examined post mortem, none showed evidence of tuberculous disease. The results for the isoniazid-treated groups ranged between the results in the normal and in the control groups. The animals which received 3 mg. of isoniazid per kg. three days a week, 2 mg. per kg. daily, 5 mg. per kg. one day a week, or 4 mg. per kg. three days a week showed progressively less tuberculosis; while those which received 5, 4, or 3 mg. per kg. daily, or 10 or 5 mg. per kg. three days a week, were very like the normal animals. Only a few of the 178 animals that had received isoniazid in a daily dose of 5, 4, or 3 mg. per kg. showed evidence at death of tuberculosis: 3 were classified as having 2- to 4-plus disease and 5 as having 1-plus or plus-minus disease. Even less tuberculosis was found among

TABLE 2

PROJECT D: OUTLINE OF EXPERIMENTAL GROUPS, PROCEDURES, AND NUMBER OF GUINEA PIGS SURVIVING OR SACRIFICED AT SPECIFIED WEEKS AFTER INOCULATION OF VIRULENT TUBERCLE BACILLI (OR SALINE)

Group	Isoniazid*		Challenge (C) or Saline (S)	Number of Animals at Specified Weeks										
				Surviving									Sacrificed†	
				0	4	6	10	14	20	26	32	39	0-10	25-26
	mg./kg./day	*weeks*												
Normal	—	—	S	96	86	78	67	62	53	50	46	42	11	2
Control	—	—	C	144	60	18	0	—	—	—	—	—	50	—
1	3	2	C	144	130	105	66	49	38	23	11	9	50	10
2	3	4	C	144	128	112	72	59	55	43	30	24	41	10
3	3	6	C	120	108	101	73	62	55	49	39	37	32	10
4	3	8	C	120	113	101	82	71	63	58	46	40	22	10
5	3	10	C	96	84	74	59	53	48	42	31	28	17	10
6	3	39	C	96	90	78	63	50	47	45	35	34	24	10

* Given daily, starting 48 hours before challenge

† For bacteriologic and pathologic examination for tuberculosis

the 120 animals given 10 or 5 mg. per kg. of isoniazid three days a week: none of those that died showed 2- to 4-plus tuberculosis and only 2 were classified as plus-minus or 1-plus.

Results of the post-mortem examinations support the evidence provided by the mortality data on the effect of the various isoniazid regimens: during five months of observation, isoniazid given in sufficient dosage not only prevented a large inoculation with virulent tubercle bacilli from killing the animals, but also prevented the development of gross pathologic signs of tuberculous disease.

Variations in Duration of Isoniazid Administration (Project *D*)

The next project was set up to study the effect of varying the duration of isoniazid administration.

In this experiment (Project *D*) isoniazid in a daily dose of 3 mg. per kg. was given to six groups of animals and, as shown in table 2, the drug was given throughout the experiment to one group but was given to the others for only two, four, six, eight, or ten weeks after the inoculation. A total of 960 random-bred male and female guinea pigs were randomly allocated into eight groups, one of which served as the normal group and another as the control group. Isoniazid was started forty-eight hours before the inoculation, which again consisted of an intraperitoneal injection of 0.5 ml. of a diluted liquid Tween-albumin suspension of H37Rv. In this project, the plate counts showed 8.5×10^6 viable bacillary units per 0.5 ml. of the suspension. The experiment was started on June 7, 1955, and was terminated after thirty-nine weeks when all survivors were withdrawn for another project.

Mortality: Survival curves for the eight groups of guinea pigs are presented in figure 7. The control animals died very rapidly, as shown by the curve on the left: 50 per cent of the animals were dead within four weeks and the few still alive after eight weeks were all sacrificed. Animals given isoniazid for only two

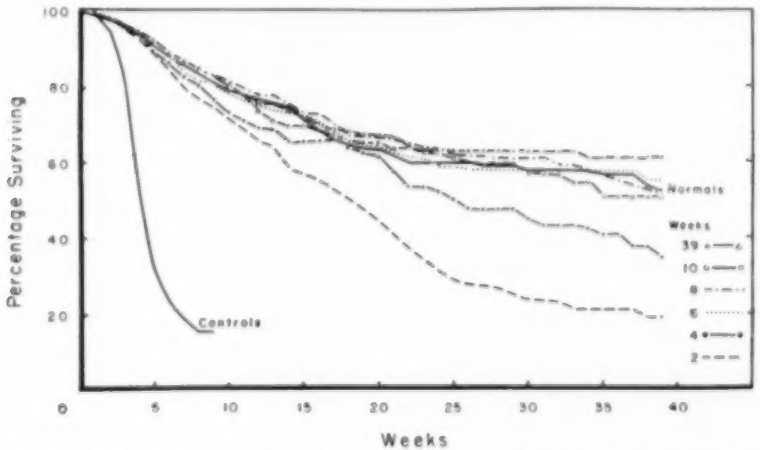

FIG. 7. *Project D:* percentage of guinea pigs alive at weekly intervals after inoculation of virulent tubercle bacilli (or saline), according to duration of isoniazid regimen (percentages adjusted for animals sacrificed).

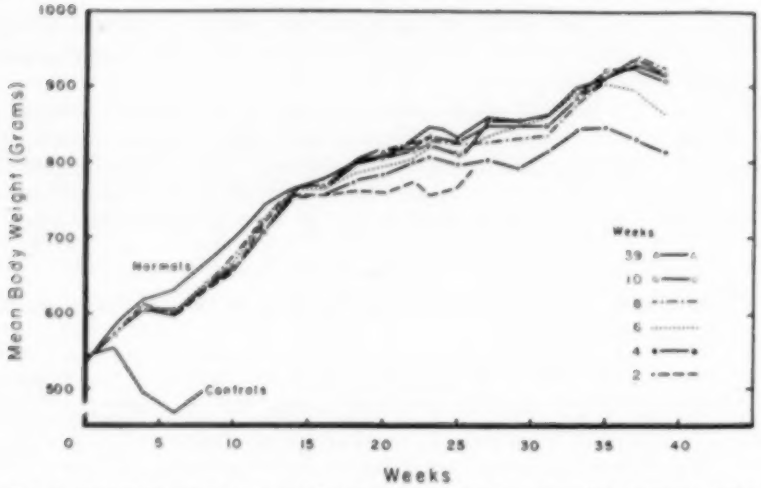

FIG. 8. *Project D:* mean body weight of guinea pigs alive at weekly intervals after inoculation of virulent tubercle bacilli (or saline), according to duration of isoniazid regimen.

weeks began to die more rapidly than the normal animals as early as the fifth week, and by the end of the experiment less than 20 per cent were still alive. The mortality of animals given the drug for four weeks showed a consistent increase after the eighteenth week, and 35 per cent were still alive after thirty-nine weeks. Animals in groups in which isoniazid was given for six, eight, or ten weeks, or for thirty-nine weeks, died at approximately the same rate as the normal animals throughout the nine-month period of observation in this experiment.

Growth in body weight: The mean body weight of the surviving animals in each group at weekly intervals is given in figure 8. Starting with a mean of about 540 gm., the control animals lost weight rapidly and by the eighth week after the inoculation when the few survivors were sacrificed they weighed on the average only 500 gm. With minor variations the normal animals showed a steady increase throughout the course of the experiment. The mean weights of all groups which received isoniazid were somewhat below those of the normal animals in the first thirteen weeks; thereafter, the weight of animals that received the drug for six, eight, ten, or thirty-nine weeks was very much like that of the normal animals, while animals that received the drug for only two or four weeks tended to weigh less and to show more variation as the number of living animals decreased. In general, growth in body weight appears to corroborate the mortality data shown in figure 7.

Tuberculin sensitivity: Mean sizes of the skin reactions to intradermal tests with 0.005 mg. of PPD-S are shown in figure 9 for all groups except the normal animals. Tests were given to half the animals in each group each week from the third to the tenth week after the inoculation, then to all surviving animals in

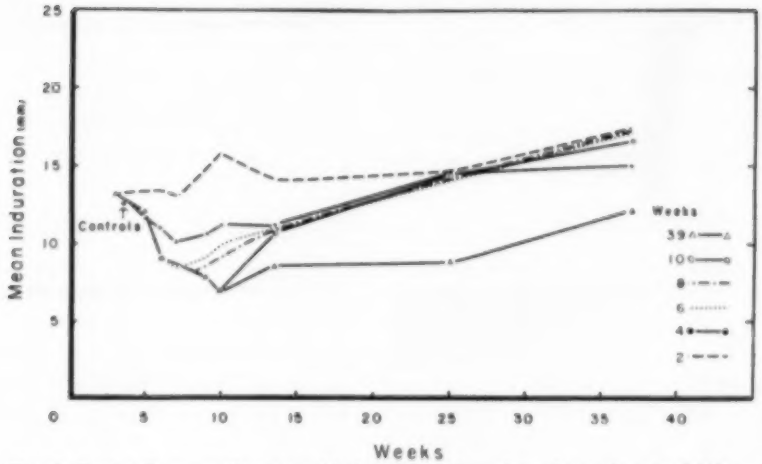

FIG. 9. *Project D:* mean diameter of induration of intradermal reactions to 0.005 mg. of PPD-S for guinea pigs alive at specified intervals after inoculation of virulent tubercle bacilli, according to duration of isoniazid regimen.

each group at thirteen, twenty-five, and thirty-seven weeks. From a mean of 13 mm. at the third week, the sizes of the tuberculin reactions fell rapidly for all but the group in which isoniazid had been discontinued one week previously. As each group was taken off the drug, however, the sizes of the tuberculin reactions began to increase and by the twenty-fifth week the means were nearly the same for all groups except the one still getting isoniazid. With continuous administration of isoniazid, the degree of tuberculin sensitivity decreased steadily during the first ten weeks; yet after that time, instead of a further decrease, the sensitivity showed a slight rise but remained at a level appreciably below that of the other groups.

Gross tuberculous pathology: Post-mortem examinations of the 437 animals that died during the thirty-nine-week observation period in this experiment (Project *D*) are summarized in the series of graphs in figure 10. Unfortunately, a rather high proportion of the animals that died were not examined post mortem primarily because sufficient personnel was sometimes not available if animals died during a week end. Of the 94 control animals that died before the eighth week, 86 were examined post mortem: 55 showed lesions classified as 2- to 4-plus tuberculosis; 26 were classified as plus-minus or 1-plus, and 5 were reported negative for tuberculosis. For the normal group, all but 2 of the 41 animals examined after death were negative for tuberculosis. One was reported as showing signs of extensive tuberculous disease and the other was classified as having 1-plus disease; yet both had failed to react to tuberculin. Their classification as tuberculous can be taken as a measure of experimental error, which includes observational error in doing "blind" post-mortem examinations.

Autopsy reports on animals that received isoniazid for only two weeks showed

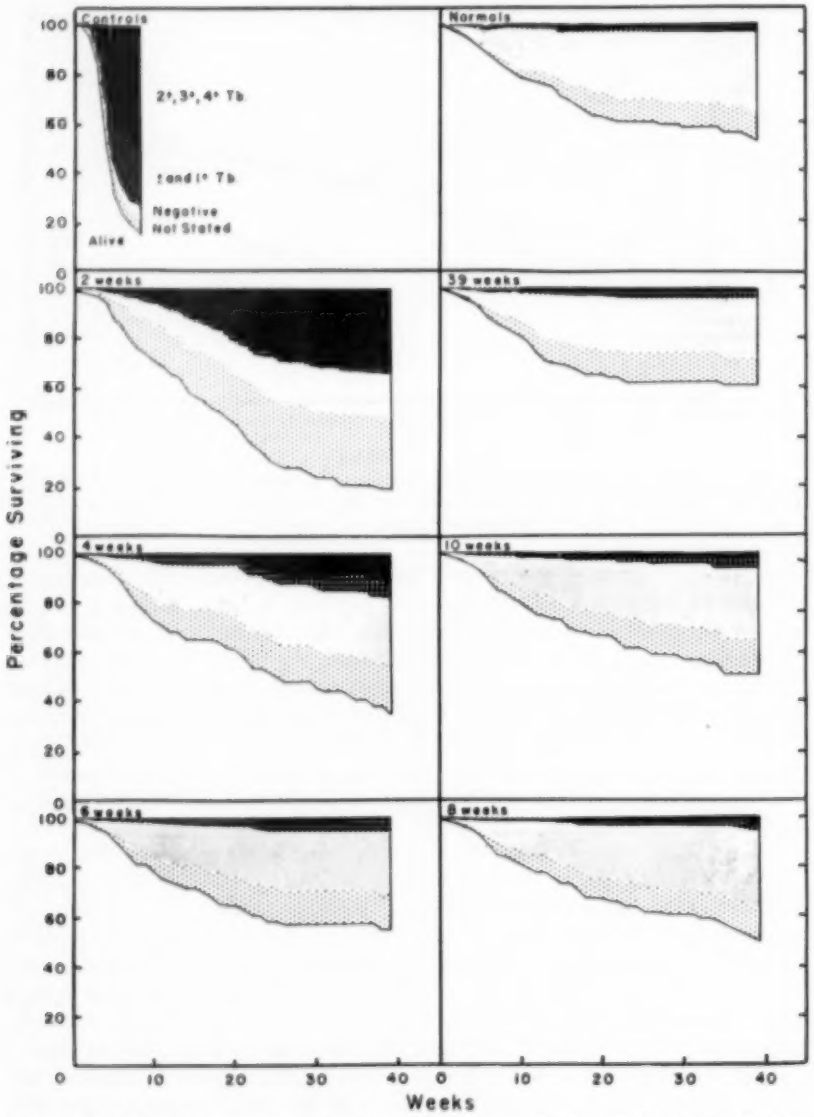

FIG. 10. *Project D:* percentage of guinea pigs alive or dead at weekly intervals after inoculation of virulent tubercle bacilli (or saline), according to duration of isoniazid regimen; the dead classified according to gross evidence of tuberculosis at autopsy (percentages adjusted to exclude animals sacrificed).

that the majority were classified as having 2- to 4-plus tuberculosis. Although nearly half of the animals that received the drug for four weeks showed lesions, only one-fourth had extensive tuberculosis. In striking contrast, very little tuberculosis was found among animals that died in the groups which received isoniazid for six weeks or longer. In fact, in those four groups in which mortality was no greater than for the normal animals, no more tuberculosis was found than in the normal group.

Further Variations in Dose and Frequency of Isoniazid Administration (Project *E*)

The next experiment (Project *E*) was designed to study further the effects of intermittent administration of isoniazid and to investigate the earlier observation that during an isoniazid-treated massive first inoculation the animals apparently develop resistance to a subsequent *untreated* inoculation.

The project involved 960 random-bred male and female guinea pigs allocated at random into the seven groups shown in table 3. The control group for the treated (first) inoculation contained 72 animals, while the normal group contained 288. Each of five groups of 120 animals received a specified dose of isoniazid for forty-eight hours before and forty-eight hours after the inoculation, then daily in *Group 1*, three days a week (Wednesday, Saturday, and Sunday) in *Group 2*, one day a week in *Groups 3* and *5*, and two days a week (Monday and Tuesday) in *Group 4*. The drug was discontinued in all groups at the end of four weeks.

Two weeks after the drug had been discontinued, that is, six weeks after the first inoculation, a second inoculation was given to all animals in *Groups 1* through *5*; and a new control group was obtained by inoculating 69 animals selected at random from the normal group. The 196 animals left in the normal group remained uninfected and untreated. The

TABLE 3

PROJECT E: OUTLINE OF EXPERIMENTAL GROUPS, PROCEDURES, AND NUMBER OF GUINEA PIGS SURVIVING OR SACRIFICED AT SPECIFIED WEEKS AFTER INOCULATION OF VIRULENT TUBERCLE BACILLI (OR SALINE)

Group	Isoniazid*		Challenge (C) or Saline (S)		Number of Animals at Specified Weeks									
					Surviving								Sacrificed†	
			First at 0 Weeks	Second at 6 Weeks	0	4	6	10	16	22	28	34	24–25	31–32
	mg/kg	*days/wk*												
Normal	—	—	S	S	288	272	196	191	111‡	104	94	88	2	2
				C	—	—	69§	32	17	8	6	3	—	—
Control	—	—	C	—	72	31	15	3	1	1	0	—	—	—
1	3	7	C	C	120	114	112	92	74	54	28	6	15	14
2	5	3	C	C	120	115	112	101	85	64	29	10	14	14
3	10	1	C	C	120	108	97	88	70	51	22	4	14	14
4	10	2	C	C	120	113	110	101	89	76	41	16	14	14
5	20	1	C	C	120	114	109	103	84	67	40	16	14	14

* Given for 4 weeks starting 48 hours before challenge

† For bacteriologic and pathologic examinations for tuberculosis

‡ 63 animals withdrawn at 15 weeks for another project

§ 69 animals withdrawn from normal group at 6 weeks to serve as controls for second challenge

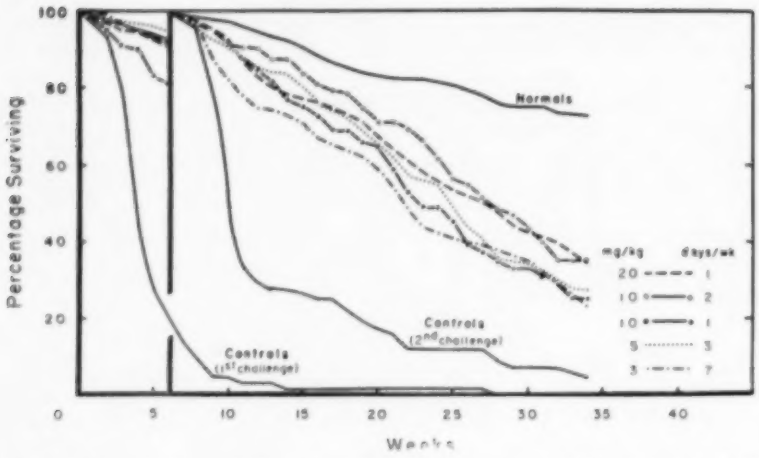

FIG. 11. *Project E:* percentage of guinea pigs alive at weekly intervals after a first (0 weeks) and second (6 weeks) inoculation of virulent tubercle bacilli (or saline), according to dosage of isoniazid of four weeks' duration (percentages adjusted for animals sacrificed).

technique of inoculating the animals was that used throughout all of the projects; and the infecting dose was 6.5×10^5 viable bacillary units of H37Rv per 0.5 ml. for the first inoculation and 6.0×10^5 for the second. The experiment was started on August 25, 1955, and was terminated after thirty-four weeks.

Mortality: The survival curves for this experiment (Project *E*) are shown in figure 11. All curves start at 100 per cent at the time of the first inoculation and the curve for the control animals is continued until the last animal in the group died during the twenty-seventh week. When the second inoculation is given six weeks after the first, the curves for all but the first control group are put back to 100 per cent, and the curve for the second control group is introduced at that point.

More than 50 per cent of the animals in the first control group were dead by the end of the fourth week and nearly 80 per cent by the end of the sixth week; whereas animals which received isoniazid, except for those given 10 mg. per kg. one day a week, survived as well as the untreated, uninfected normal animals during the first six weeks. The excessive mortality in the group given 10 mg. per kg. one day a week was caused by an intercurrent nontuberculous infection that affected animals in certain cages.

Following the second challenge inoculation, more than 50 per cent of the animals in the new control group were dead within four weeks. In contrast, the animals that had previously received isoniazid for four weeks and were then reinoculated without receiving further drug, died much less rapidly than the control animals although their mortality was greater than for the normal group. Although the differences in mortality among groups were relatively small, the mortality was greatest for the group previously given 3 mg. of isoniazid per kg.

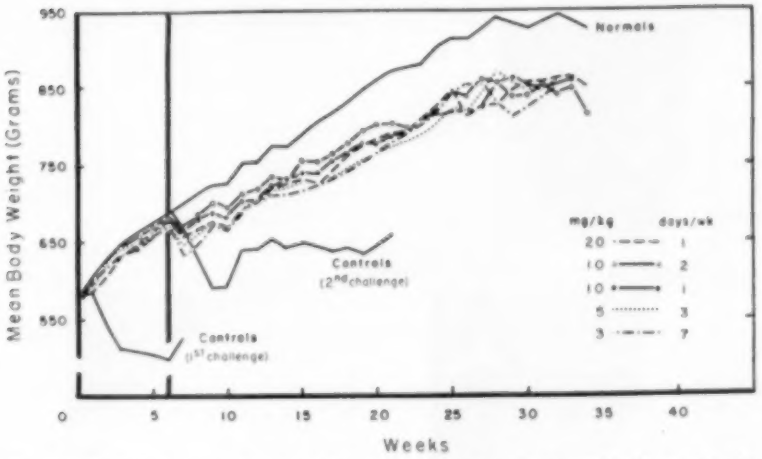

FIG. 12. *Project E:* mean body weight of guinea pigs alive at weekly intervals after a first (0 weeks) and second (6 weeks) inoculation of virulent tubercle bacilli (or saline), according to dosage of isoniazid of four weeks' duration.

daily, and least for the group previously given 10 mg. per kg. two days a week. Taken altogether, the results show that large doses of isoniazid given intermittently during the first infection were slightly more effective than small frequent doses in prolonging life after an untreated challenge infection.

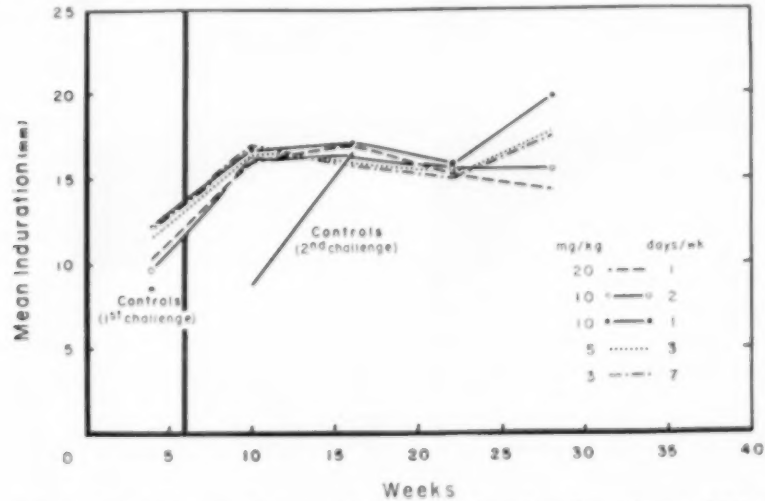

FIG. 13. *Project E:* mean diameter of induration of intradermal reactions to 0.005 mg. of PPD-S for guinea pigs alive at specified intervals after a first (0 weeks) and second (6 weeks) inoculation of virulent tubercle bacilli (or saline), according to dosage of isoniazid of four weeks' duration.

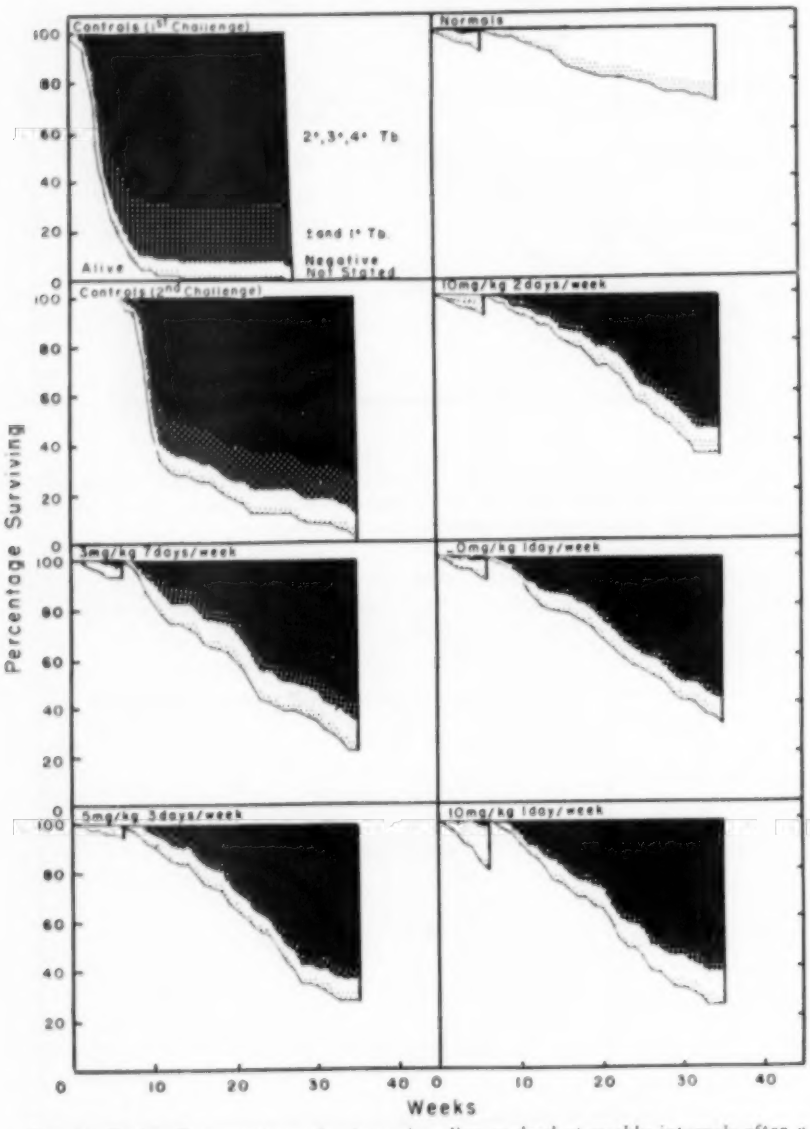

FIG. 14. *Project E:* percentage of guinea pigs alive or dead at weekly intervals after a first (0 weeks) and second (6 weeks) inoculation of virulent tubercle bacilli (or saline), according to dosage of isoniazid of four weeks' duration; the dead classified according to gross evidence of tuberculosis at autopsy (percentages adjusted to exclude animals sacrificed).

Growth in body weight: The mean weight of the animals in this experiment (Project *E*) at the time of the first inoculation was close to 570 gm. with very little difference among the seven groups (figure 12). During the first six weeks of the project, all groups except the control animals gained steadily.

Growth curves for the various groups after the sixth week provide rather striking confirmation of the results shown in figure 11. The new (second) control group showed the rapid loss characteristic of infected untreated animals, and the normal animals gained steadily without interruption. The previously treated animals showed an initial loss after the second infection, followed by a continuous gain throughout the rest of the observation period. Weight curves for the five groups were very similar.

Tuberculin sensitivity: Results of intradermal tuberculin tests with 0.005 mg. of PPD-S are shown in figure 13 as the mean size of the reactions of each group (except the normal animals) at four, ten, sixteen, twenty-two, and twenty-eight weeks. Four weeks after the first inoculation, the mean size of the tuberculin reactions was 8 mm. for the surviving control animals, 10 mm. for the groups given 20 mg. of isoniazid per kg. one day a week or 10 mg. per kg. two days a week, and approximately 12 mm. for the other three groups. At the ten-week testing session (four weeks after the second inoculation) the mean for the new control group was also 8 mm., but the means for other groups were close to 17 mm. Little change from the ten-week results was observed at either sixteen or twenty-two weeks. By the twenty-eighth week, however, differences appeared among the groups. The tuberculin sensitivity of the groups given 20 mg. per kg. one day a week or 10 mg. per kg. two days a week remained approximately the same as before, while the other three groups showed some increase in degee of sensitivity—an increase that appears to correspond with the slightly higher mortality in those groups.

Although the factors affecting tuberculin sensitivity are apparently complex, the increase in degree of sensitivity between the fourth and tenth weeks in this project can probably be attributed to the effects of both the withdrawal of the drug at the fourth week and the second inoculation at the sixth week.

Gross tuberculous pathology: Results of the post-mortem examinations of animals that died during the experiment are summarized in figure 14 for both the first and the second inoculations. As expected, most of the control animals showed extensive tuberculosis, while no evidence of the disease was found in the normal animals. During the first six weeks of the project only a very few animals that had received isoniazid were reported on autopsy as having signs of tuberculosis.

As discussed in connection with figure 11, animals that had received isoniazid during their first virulent infection died, after their untreated challenge, more rapidly than the normal animals but less rapidly than those in the second control group. When they did die, however, they showed approximately the same post-mortem evidence of tuberculosis as the control animals, irrespective of their previous isoniazid regimen. *Under the conditions of this experiment*, it thus appears that the resistance that developed in guinea pigs during the course of an

isoniazid-treated first infection only slowed the progress of the untreated reinfection but did not prevent its lethal effects.

DISCUSSION

The inoculation of relatively large numbers of virulent tubercle bacilli into random-bred guinea pigs can be expected to produce a tuberculous infection which progresses to tuberculous disease and eventually to death. The primary purpose of the present studies has been to investigate the effect of isoniazid on that sequence of events. While the subject is a broad and complex one which may be studied from many different aspects, the projects carried out thus far represent a step-by-step approach in studying some of the more obvious variables, and the results must be interpreted within the framework of the experimental situation.

In studying this question, it is probably important at the outset to distinguish between prevention of tuberculous infection and prevention of tuberculous disease. While it may be argued that the two are synonymous in a strict, academic sense, many workers would probably agree that tuberculin sensitivity, as the only evidence of infection in an individual, is usually distinguishable from the signs commonly associated with progressive disease. Such a distinction is made in interpreting the results of the present studies.

In the three projects described in this report, the administration of isoniazid did not prevent evidence of tuberculous infection after a *massive* inoculation of virulent tubercle bacilli. All of the animals developed and retained strong sensitivity to tuberculin. Yet isoniazid, when given in certain dosage regimens for certain periods of time, apparently can be highly effective in preventing tuberculous disease and death. In these experiments, prevention has been considered effective if, during the period of observation, animals inoculated with virulent tubercle bacilli survived as long as normal, uninfected animals; and if they not only survived but apparently remained healthy for a prolonged observation period after isoniazid was discontinued. These criteria of effectiveness have been fulfilled by the results obtained with a number of different isoniazid regimens.

Isoniazid dosage regimens of 3 mg. per kg. daily, 5 mg. per kg. three days a week, 10 mg. per kg. two days a week, or 20 mg. per kg. only one day a week were of approximately equal effectiveness and, among those studied so far, represent the smallest dosage regimens that produce such effects. Other regimens, i.e., smaller amounts of drug or the same amount given at less frequent intervals, only slowed the progress of disease and did not prevent the ultimately lethal effects of the tuberculous infection. One of the critical findings, however, is that a given amount of drug appears to be more effective in large, less frequent doses than in small, more frequent doses (4–6). For example, a total weekly dose of 14 mg. per kg., given as 2 mg. per kg. daily, was relatively ineffective; whereas 15 mg. per kg., given as 5 mg. per kg. three days a week, was highly effective.

The length of time required for effective prophylaxis may be relatively short. In the most definitive study carried out so far, administration of isoniazid for

six weeks prevented the appearance of tuberculous disease during an eight-month period of observation after the drug was discontinued.

Observations on tuberculin sensitivity suggest that administration of isoniazid, particularly of the larger doses of the drug, may depress the degree of sensitivity. During the early weeks after the inoculation, the degree of sensitivity, as measured by the mean size of the tuberculin reactions of a group, did not differ greatly between the control animals and the animals which received isoniazid. But, when isoniazid was continued, the degree of sensitivity often tended to fall and to remain at a low level until the drug was stopped; then it gradually rose and regained its initial level. In some instances, however, depression of sensitivity with continued administration of isoniazid was not evident. And in other instances there were indications that a rising level of sensitivity was related to a fall in the mortality curve. While the effect of isoniazid on tuberculin sensitivity thus appears to be complex and variable, one of the significant findings in the present studies is that none of the dosage regimens prevented the development of tuberculin sensitivity—evidence that isoniazid controlled or modified, rather than eradicated, a large first infection.

Post-mortem examination for gross evidence of tuberculous disease in animals that died during the course of the experiments corroborate the mortality data on the prophylactic effect of isoniazid. The control animals died rapidly, as expected, and most of them showed evidence of extensive tuberculous disease; whereas animals given one of several different but apparently sufficient doses of isoniazid, and the same massive inoculation as the control animals, died no more rapidly than the normal uninfected animals and rarely were reported as grossly tuberculous. Animals given smaller, apparently insufficient doses died more rapidly than the normal animals but less rapidly than the control animals, and at death frequently showed evidence of extensive tuberculosis. Thus, the findings for the various groups reveal an inverse quantitative relation between insufficient doses of isoniazid, on the one hand, and tuberculous disease and death, on the other.

Another finding described in the earlier report and confirmed in one of the present projects is the evidence of acquired resistance to a second virulent infection in animals previously infected while receiving isoniazid. After completing a course of isoniazid sufficient to prevent tuberculous disease and death, animals reinfected without resuming treatment appear to have developed an appreciable degree of protection against the tubercle bacillus. This finding is interpreted as indicating that the isoniazid treatment did not nullify the antigenic effects of the first infection. It should be noted in this connection that both the first and second inoculations consisted of some half a million virulent organisms, and similar results might not be expected with the smaller inocula now being studied.

SUMMARY

Results are reported of three projects designed to investigate the effects of various dosage regimens of isoniazid in preventing tuberculous disease in guinea pigs. The drug was administered in the animals' drinking water, in doses ranging

from 2 to 20 mg. per kg., in frequencies ranging from one to seven days a week, and for periods ranging from two to thirty-nine weeks. For each project, isoniazid was started forty-eight hours before the animals were given an intraperitoneal inoculation of one-half to one million viable bacillary units of H37Rv.

In confirming and extending an earlier report, the present projects show that a prophylactic regimen of isoniazid not only prevents death from tuberculosis but also prevents the appearance of gross evidence of tuberculous disease. The animals grow in body weight as well as normal animals, they become and remain sensitive to tuberculin, and they acquire some resistance against subsequent reinfection after the drug has been discontinued. Isoniazid regimens ranging from 3 mg. per kg. daily to 20 mg. per kg. only one day a week for a period of six to ten weeks appear to be equally effective minimal dosages in protecting against the initial tuberculous infection.

When used prophylactically in guinea pigs, as in the present experiments, isoniazid can apparently convert a massive inoculation of virulent tubercle bacilli into a controlled, benign, tuberculous infection.

SUMARIO

Estudios de la Prevención de la Tuberculosis Experimental con Isoniacida. II. Efectos de Diversos Regímenes Posológicos

Preséntanse los resultados de tres proyectos destinados a investigar los efectos de varios regímenes posológicos de isoniacida en la prevención de la enfermedad tuberculosa en los cobayos. La droga fué administrada en el agua de bebida de los animales, a dosis que variaban de 2 a 20 mg. por kg. de peso, en frecuencias que variaban de uno a siete días por semana y durante períodos que variaban de dos a treinta y nueve semanas. En todos los proyectos, se inició la isoniacida cuarenta y ocho horas antes de que los animales recibieran una inoculación intraperitoneal de medio millón a un millón de unidades bacilares viables de H37Rv.

Confirmando y ampliando una comunicación anterior, los proyectos actuales muestran que un régimen profiláctico de isoniacida no sólo impide la muerte por tuberculosis sino también impide la aparición de signos macroscópicos de enfermedad tuberculosa. Los animales aumentan de peso lo mismo que los animales normales, se vuelven y permanecen sensibles a la tuberculina y adquieren alguna resistencia a la reinfección subsiguiente después de suspenderse la droga. Los regímenes de isoniacida, que varían de 3 mg. diarios por kg. de peso a 20 mg. por kg. solamente un día de la semana durante un período de seis semanas, parecen constituir una dosis mínima igualmente eficaz para proteger contra la infección tuberculosa inicial.

Usada profilácticamente en los cobayos, como en los experimentos actuales, la isoniacida puede aparentemente convertir una inoculación masiva de bacilos tuberculosos virulentos en una infección tuberculosa benigna y regulada.

RESUME

Recherches sur la prévention de la tuberculose expérimentale à l'aide de l'isoniazide: II. Effets de différents schémas posologiques

Exposé des résultats de trois programmes d'investigation des effets de divers schémas d'administration de l'isoniazide dans la prévention de l'infection tuberculeuse chez le cobaye. La drogue fut administrée dans l'eau de boisson de l'animal, à doses s'échelonnant entre 2 et 20 mg/kg à intervalles variant de un à sept jours par semaine et pendant des périodes allant de deux à trente-neuf semaines. Dans chaque programme, l'administration de l'isoniazide était instaurée quarante-huit heures avant que les animaux aient reçu l'injection intrapéritonéale de 500 000 à un million d'unités bacillaires de H37Rv viables.

Le programme actuel qui confirme et étend les données d'un rapport antérieur montre que le traitement prophylactique par l'isoniazide non seulement préviennent la mort par tuberculose, mais aussi préviennent l'apparition des signes macroscopiques de la maladie tuberculeuse. Les animaux augmentent de poids comme les animaux normaux, ils acquièrent et conservent une sensibilité à la tuberculine et ils obtiennent un certain degré de résistance à la réinfection ultérieure lorsque la médication a été suspendue. L'administration d'isoniazide aux doses de 3 mg/kg à 20 mg/kg par jour, seulement une fois par semaine pendant une période de six à dix semaines paraît être la dose minima également efficace pour protége l'animal contre l'infection tuberculeuse initiale.

Quand elle est administrée préventivement chez le cobaye, comme dans l'expérimentation actuelle, l'isoniazide peut apparemment convertir une inoculation massive de bacilles tuberculeux virulents en une infection tuberculeuse limitée et bénigne.

Acknowledgment

The writers gratefully acknowledge their indebtedness to the entire laboratory staff, especially Helen Gertz, Lillian Lang, and Beatrice Swanson.

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PRIMARY MEDIASTINAL CYSTS AND NEOPLASMS IN INFANTS AND CHILDREN[1,2]

F. HENRY ELLIS, JR., AND JAMES W. DuSHANE

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The subject of mediastinal cysts and neoplasms has been an intriguing one to physician and surgeon alike. In spite of wide interest in the field, the bulk of the literature on this subject concerns adults. These lesions, however, are not uncommon in infants and children. Furthermore, there are differences in the types of lesions encountered, in their relative frequency, and in the incidence of malignant lesions in patients of this age group as compared with adults. The purpose of this paper is to emphasize some of these features.

MATERIAL

All thoracic roentgenograms made between January, 1935, and May, 1956, and showing some abnormality of the mediastinal shadow in patients less than fifteen years of age were reviewed.[3] Only those patients who were determined to have a primary mediastinal cyst or neoplasm were included in the final study. The pathologic specimens were reviewed grossly and microscopically in each instance.[4] All patients with metastatic lesions, mediastinal lymphomas or granulomas, and hyperplastic thymus glands were excluded.

OBSERVATIONS

General Considerations

Fifty-eight patients were found to have primary cysts or neoplasms of the mediastinum. Some of these patients have been referred to briefly in a previous communication (1). The nature of the lesions in the present series is indicated in table 1. The diagnosis was established in all but 2 of the patients by surgical removal or biopsy of the tumor; in 2 patients the diagnosis was made at necropsy. One of the 56 patients who underwent surgical treatment died in the hospital.

Symptoms were present in 35 of the 58 patients. Symptoms referable to the respiratory tract, namely, cough, dyspnea, and pain, were most commonly noted. In 21 patients the lesion was discovered only at the time of a routine roentgenographic examination of the thorax. In 2 others the lesion was encountered incidentally at the time of thoracotomy for an unrelated condition. Symptoms were more commonly associated with teratomatous tumors, enterogenous anomalies, and malignant lesions of all varieties than with any other type of

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[2] Presented before the Medical Session, as part of *Section 1A*, at the annual meeting of the National Tuberculosis Association, New York, New York, May 21, 1956.

[3] The majority of the roentgenograms were reviewed by Dr. John R. Hodgson of the Section of Diagnostic Roentgenology, Mayo Clinic.

[4] Dr. Lewis B. Woolner of the Section of Surgical Pathology, Mayo Clinic, reviewed the tissue.

TABLE 1

PRIMARY MEDIASTINAL CYSTS AND NEOPLASMS IN INFANTS AND CHILDREN

Lesion	Benign	Malignant	Total	
			Number	Per Cent
Neurogenic tumor			19	32.8
Ganglioneuroma	10			
Neurofibroma	4			
Neuroblastoma		4		
Neurofibrosarcoma		1		
Teratomatous tumor			16	27.6
Teratoma	8			
Dermoid cyst	5			
Teratocarcinoma		3		
Enterogenous anomaly			10	17.2
Bronchogenic cyst	5			
Esophageal cyst	2			
Gastric cyst	1			
Indeterminate cyst	1			
Duplication of alimentary tract	1			
Vascular tumor			5	8.6
Cavernous hemangioma	2			
Hemangiopericytoma	1			
Angiosarcoma		2		
Cystic hygroma	4		4	6.9
Grade 4 malignant neoplasm (unclassified)		4	4	6.9
Total	44 (76%)	14 (24%)	58	100.0

mediastinal lesion. Patients with benign neurogenic tumors were notably asymptomatic, as were patients with vascular tumors.

Certain fundamental differences exist between the incidence of the various types of lesions occurring in this group of infants and children and the incidence that is observed in adults. Seven reported series of mediastinal tumors occurring primarily in adults (2–8) are summarized in table 2. Certain liberties were taken with the classifications of these authors. Mediastinal lymphomas and granulomas were excluded, as were mesotheliomas. The last-mentioned lesions are not truly mediastinal tumors but present a special problem in themselves.

Neurogenic tumors occur with equal frequency in adults and in infants and children. Ganglioneuromas, however, are much more common in younger patients. Teratomatous tumors are relatively more common in patients of the younger age group than they are in adults. Neurogenic tumors and teratomatous tumors together make up slightly more than 60 per cent of the total group of these lesions which occur in infants and children. Enterogenous cysts occur with nearly the same frequency in both age groups. Vascular tumors and cystic hygromas occur much more frequently in infants and children than in adults, while pericardial cysts, intrathoracic thyroids and tumors of the thymus were not encountered at all in this series of infants and children. The incidence of

TABLE 2

PRIMARY CYSTS AND NEOPLASMS OF THE MEDIASTINUM

Summary of Seven Reported Series Consisting Predominantly of Adults

Lesion	Benign	Malignant	Total	
			Number	Per Cent
Neurogenic tumor	174	27	201	32.7
Teratomatous tumor	101	17	118	19.2
Enterogenous cyst			86	13.9
Bronchogenic	65			
Esophageal	6			
Gastric	3			
Enteric	2			
Indeterminate	10			
Thymoma	43	14	57	9.3
Pericardial cyst	40		40	6.5
Undifferentiated carcinoma and sarcoma		29	29	4.7
Intrathoracic thyroid	25	2	27	4.4
Miscellaneous	57		57	9.3
Total	526 (85.5%)	89 (14.5%)	615	100.0

malignancy in the series reported here (table 1), being 24 per cent, is higher than the 14.5 per cent for the seven series reviewed in table 2.

For a series of mediastinal cysts and neoplasms in infants and children, Gross (9) reported an incidence of lesions that is somewhat different from those in the present series. In his series of forty-nine cases, the predominant lesions were enterogenous cysts and duplications of the alimentary tract, while the incidence of teratomatous tumors was fairly low. He encountered a higher incidence of malignancy in his series of cases than was encountered in the present series, i.e., 34.6 per cent as opposed to 24 per cent.

Special Considerations

Neurogenic tumors: There were 19 neurogenic tumors. Ten of these were found on histologic examination to contain ganglion cells and were therefore classified as ganglioneuromas. There were four neurofibromas, one neurofibrosarcoma, and four neuroblastomas. These tumors arise from intercostal or sympathetic nerves and lie typically in the posterior gutter of the thorax. Strictly speaking, they do not arise from the mediastinum, but they are commonly included among the mediastinal tumors. They may occur on the right or left and may be located in the superior, mid, or inferior mediastinum. All of the neurogenic tumors in this series were located in the posterior mediastinum.

Ganglioneuromas are more common in children than in adults; 10 of the 14 benign neurogenic tumors were of this variety. Symptoms referable to the respiratory tract were absent, the tumor being found on routine roentgenographic examination of the thorax in each instance. One patient with a "dumb-

bell" ganglioneuroma experienced neurologic disturbances of the extremities, making walking difficult. Another had Horner's syndrome on the side of the intrathoracic lesion. A third exhibited the typical café-au-lait spots of von Recklinghausen's disease (neurofibromatosis).

Three of the 4 patients with intrathoracic neurofibromas had the stigmas of von Recklinghausen's disease, with café-au-lait spots or multiple peripheral neurofibromas, or both. Respiratory symptoms were present in only one of the 4 patients. Another patient with von Recklinghausen's disease was found at post-mortem examination to have a neurofibrosarcoma of the mediastinum. This case was reported by Maksim and associates (10). Surgical excision of the intrathoracic tumor was effected in all but one of the remaining 14 patients; the diagnosis in this patient, who had von Recklinghausen's disease and an intrathoracic tumor, was based on biopsy of a peripheral nodule.

On thoracic roentgenograms, ganglioneuromas tend to appear as elongated lesions and may extend over a distance of several vertebrae (figure 1) with a broad base along the mediastinum. Typically, neurofibromas tend to be more rounded in outline. However, the tumors encountered in this series which were associated with diffuse neurofibromatosis were multilobular and quite extensive. Both ganglioneuromas and neurofibromas produce lesions of varying density, as seen on thoracic roentgenograms. Calcium can rarely be demonstrated with the roentgenogram although it may be seen on section of the gross specimen. These tumors may produce erosion or deformities of the ribs or thoracic vertebral bodies, separation of the ribs, and enlargement of the intervertebral foramina. One or more of these changes were present in 5 of the 14 cases.

Because of the extensiveness of these tumors and their multiple extensions, complete surgical removal may be difficult. However, there have been no recurrences in this group of patients. Thoracic scoliosis of moderate to marked degree developed in 3 of the 13 patients who underwent surgical removal of the intrathoracic lesion. These are the only patients in the entire group under review who have had this complication. All 3 of these patients had erosion and deformities of the vertebral bodies and intervertebral foramina.

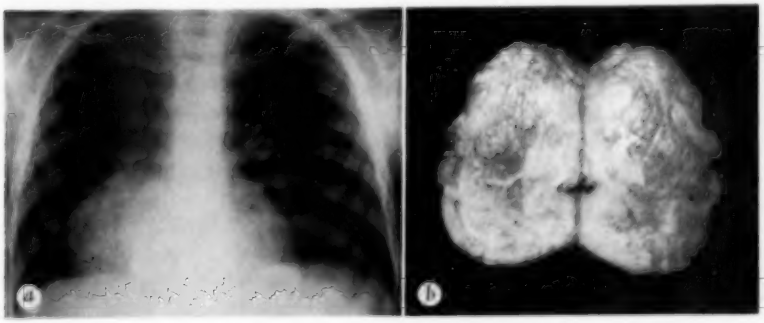

FIG. 1. *a*. Postero-anterior thoracic roentgenogram demonstrating right-sided ganglioneuroma in a 4-year-old boy. *b*. Cut section of gross specimen.

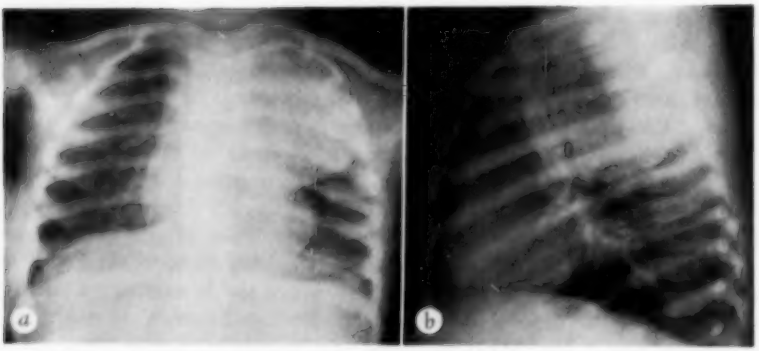

FIG. 2. Thoracic roentgenograms of 18-month-old girl with mediastinal neuroblastoma. Note multiple areas of calcification. *a*. Postero-anterior projection. *b*. Lateral projection.

Four of the 5 patients with malignant neurogenic tumors had neuroblastomas. These patients were younger than the other patients with neurogenic tumors, all but one being 18 months of age or younger. Again, in contrast to the other patients in this group, respiratory symptoms were common and thoracic pain and fever were also noted. Thoracic roentgenograms were not diagnostic. In one patient 18 months of age, evidence of multiple areas of calcification was noted in the thoracic roentgenogram (figure 2).

The tumor was completely removed in 2 of the 4 patients with neuroblastoma. Residual tumor tissue was subjected postoperatively to X-ray therapy in 2 patients. Although the prognosis is usually poor, only one of these 4 patients is dead. One was living when last heard from 10¾ years after operation. The other 2 were alive 1½ years and 4 months postoperatively.

Teratomatous tumors: Each of the 16 patients with teratomatous tumors underwent surgical excision of the tumor. A 5-week-old child died immediately following removal of a huge intrathoracic tumor.

In contrast to patients with neurogenic tumors, all but one of these patients complained of symptoms, the most common being cough, pain, and dyspnea. One patient sought medical advice because of a mass in the neck. This proved at operation to be a cervical extension of an anterior mediastinal teratoma.

These tumors lie typically in the anterior mediastinum, and on thoracic roentgenograms they appear as fairly dense masses occasionally containing amorphous deposits of calcium. The calcium appears as scattered masses rather than as diffuse small densities. The margins of the tumors are quite sharp and well defined. While the tumors may occur on either side of the thorax, they were located more commonly on the right in the group under review. In only one of the 16 cases was the lesion found to be located posteriorly (figure 3*a* and *b*).

The mass may assume extremely large proportions and may practically fill one of the two thoracic cavities, as it did in 7 of the 16 cases. Surgical removal in these cases may be difficult. A marked inflammatory reaction is not uncom

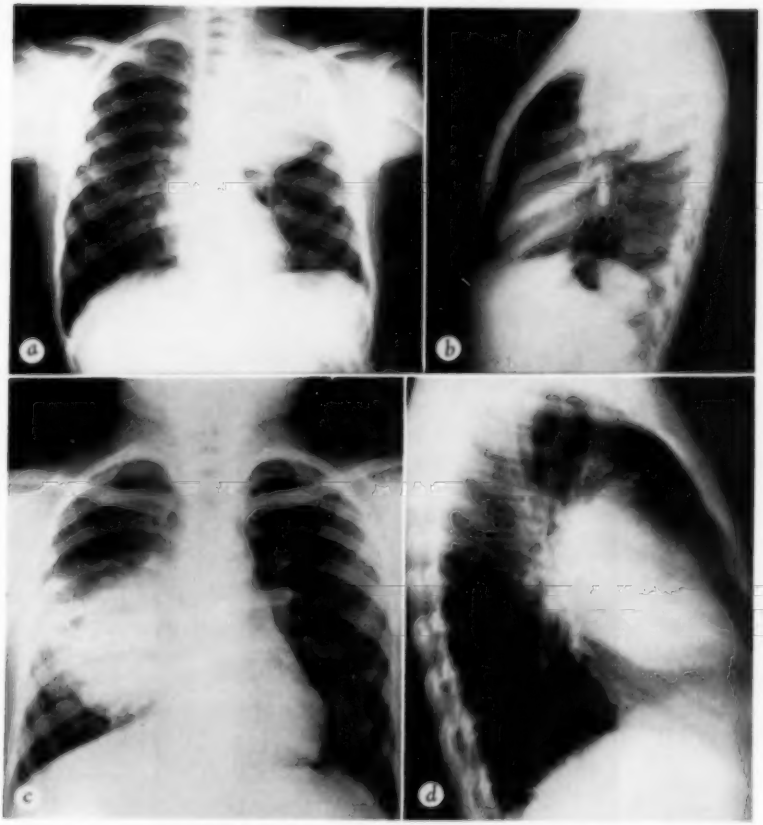

FIG. 3. *a*. Postero-anterior thoracic roentgenogram of an 8-year-old girl with a posteriorly located teratoma. *b*. Lateral projection of same patient represented in *a*. *c*. Postero-anterior thoracic roentgenogram of an anterior mediastinal teratoma in an 11-year-old girl. Tumor has perforated into the lung. *d*. Lateral projection of same patient as represented in *c*.

monly encountered about the tumor, adding to the difficulty of removal. In 3 instances perforation of the lesion had occurred, either into the lung or into the thoracic wall. In 2 of these 3 cases it was necessary to remove a portion of the involved lung (figures 3*c* and *d* and 4*a*).

Pathologically, these lesions are either composed primarily of dermal elements or they are characterized by their multidermal composition. Five of the sixteen tumors belonged to the former variety and were characteristically cystic in nature, containing varying amounts of sebaceous material and hair. There were eight benign teratomas, being composed not only of ectodermal elements but also containing neural tissues, endodermal derivatives, segments of intestinal tissue, particularly pancreas, and masses of mesodermal tissue such as cartilage

FIG. 4. *a*. Gross specimen removed from patient whose thoracic roentgenograms are pictured in figure 3*c* and *d*. Middle lobe at left, teratoma at right. *b*. Cut section of teratocarcinoma removed from 3-year-old boy whose thoracic roentgenogram is pictured in figure 5.

and smooth muscle. Some of these multidermal teratomas were predominantly cystic, while others were predominantly solid with only occasional cystic spaces.

Of particular interest are the 3 cases in which malignancy developed in teratomas (figures 4*b* and 5). In each instance the malignant tumors arose from glandular epithelium, predominantly papillary in one case. Two of these patients died five months and sixteen months, respectively, after operation. The third was still alive when last heard from four years after operation.

Enterogenous anomalies: Ten patients were found to have intrathoracic enterogenous anomalies of various sorts. Lesions of this type are congenital and may result from the pinching off of a portion of endoderm of the foregut or its tracheobronchial branches during developmental life.

These anomalies may assume various forms. They may be spherical and cystic, in which case the term "enterogenous cyst" is appropriate. Nine of the lesions in the present series were of this category. A further subdivision of this category of enterogenous cysts may be made, depending on the microscopic appearance of the lining of the wall of the cyst. There were five bronchogenic cysts. These cysts were lined with ciliated epithelium, frequently contained mucous glands and cartilage in their walls, and were filled with a thick, mucoid material. There were two esophageal cysts lined with stratified squamous epithelium, one gastric cyst lined with gastric mucosa, and one cyst of indeterminate nature with a destroyed epithelial lining.

A second category of such anomalies consists of those elongated tubular structures that resemble a portion of the gastrointestinal tract in external appearance. Their lining mucous membrane is similar to that of some portion of the alimentary tract and they may be separate from, attached to, or communicating with a portion of the alimentary canal. Anomalies of this type have been referred to in the literature as "duplications of the alimentary tract." There was one example

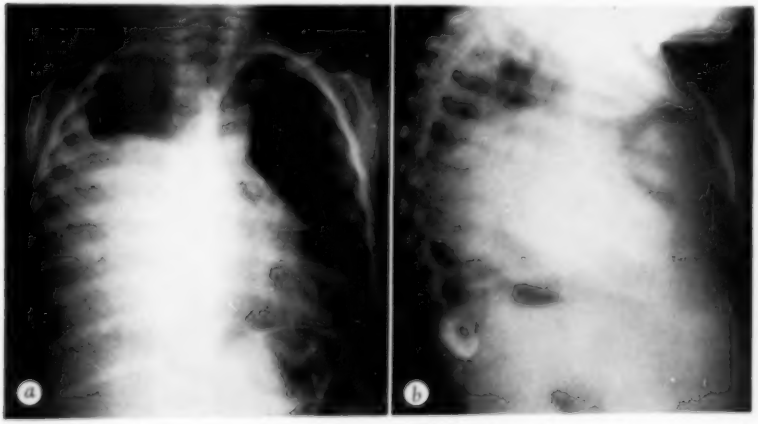

FIG. 5. Thoracic roentgenogram of patient with teratocarcinoma. Gross specimen is pictured in figure 4*b*. *a*. Postero-anterior projection. *b*. Lateral projection.

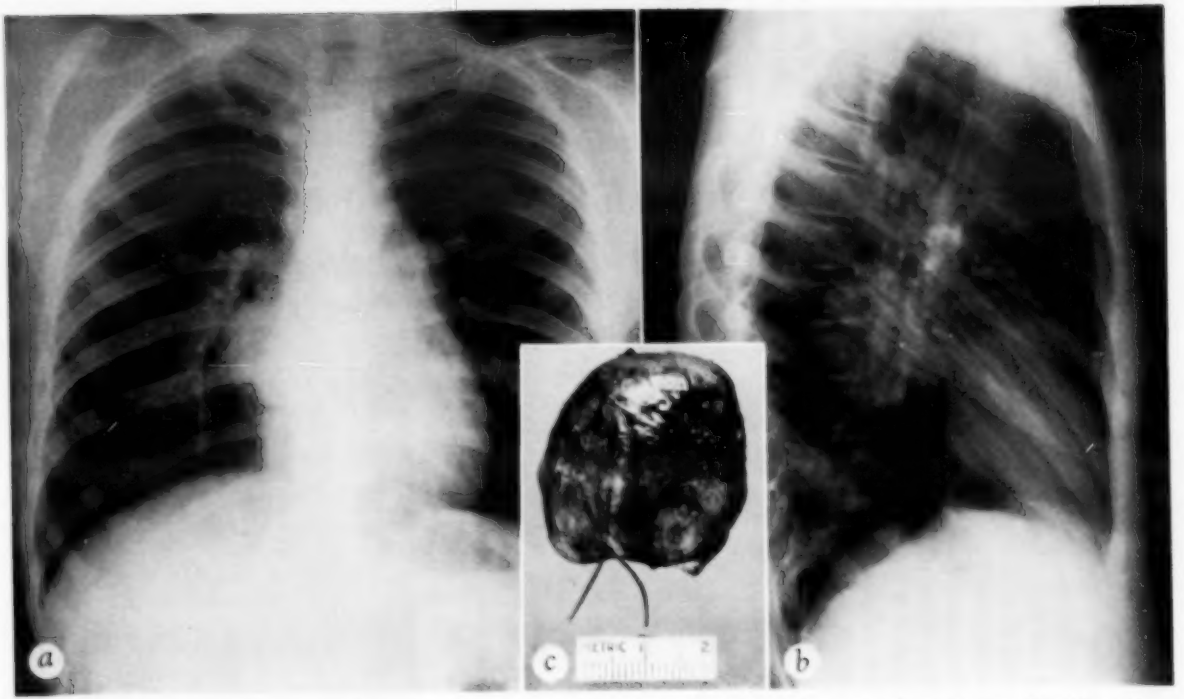

FIG. 6. Thoracic roentgenograms and gross specimen of bronchogenic cyst in mid mediastinum of an 11-year-old girl. *a*. Postero-anterior projection. *b*. Lateral projection. *c*. Gross specimen.

of this type of anomaly in the present series of cases. The patient, a 3½-month-old boy, had a history of anemia, diarrhea, and vomiting. Thoracic roentgenograms revealed a lesion in the right lower part of the thorax. At operation a duplication of the alimentary tract was found, partially lined with gastric mucosa and containing a perforating hemorrhagic peptic ulcer. It communicated with the small intestine below the diaphragm. This case has been reported in detail elsewhere (11).

Enterogenous cysts may produce marked symptoms of respiratory impairment. This was true of three of the five bronchogenic cysts and one of the two esophageal cysts. The remaining two enterogenous cysts were asymptomatic. In adults, lesions of this type are more commonly asymptomatic. Symptoms are due to compression of the tracheobronchial tree, to which these lesions may be attached. In 4 patients with symptoms, there were, in addition, compression and distortion of the esophagus although symptoms of dysphagia were absent.

Enterogenous cysts present a constant roentgenographic appearance (figure 6). They tend to lie in the mid mediastinum, particularly in the region of the bifurcation of the trachea, although they may occur posteriorly. They are sharply circumscribed, quite dense, and uniformly oval. The association between enterogenous cysts and anomalies of the vertebral column has been emphasized (12). In the present series of cases, however, vertebral anomalies were noted only in the patient with duplication of the small intestine and stomach communicating with the small bowel.

Surgical excision was readily effected in all cases. The close adherence of bronchogenic cysts to the trachea or bronchi, or both, may add to the difficulty of dissection. In one case there was a small bronchial communication connecting the bronchogenic cyst to the right main bronchus. One esophageal cyst lay within the muscular wall of the esophagus.

Vascular tumors: Of considerable interest are the five vascular tumors encountered in this series of cases. These undoubtedly constitute one of the rarest of mediastinal tumors, only occasionally being mentioned even in reports of large series of cases (8). The relatively high incidence in the present series, restricted to infants and children, is significant. There were two cavernous hemangiomas, one of which has been reported (13), one hemangiopericytoma, which also has been reported (14), and two angiosarcomas.

Four of the patients were asymptomatic. One patient with a malignant lesion had experienced thoracic pain and loss of weight prior to operation. In no instance was the diagnosis made preoperatively. The thoracic roentgenogram presents few special characteristic features. Vascular tumors may lie at any level in the mediastinum, from the thoracic inlet to the diaphragm. In all 5 of the cases in the present series, the vascular tumors were located in the upper portion of the thorax. They presented a uniformly rounded appearance of moderate density. Calcium was present in the tumor of only one patient, who had a cavernous hemangioma (figure 7). This represented a phlebolith within the tumor. One feature which has characterized the vascular tumors reported in the literature was observed in all but one of the present cases, namely, an anterior medias-

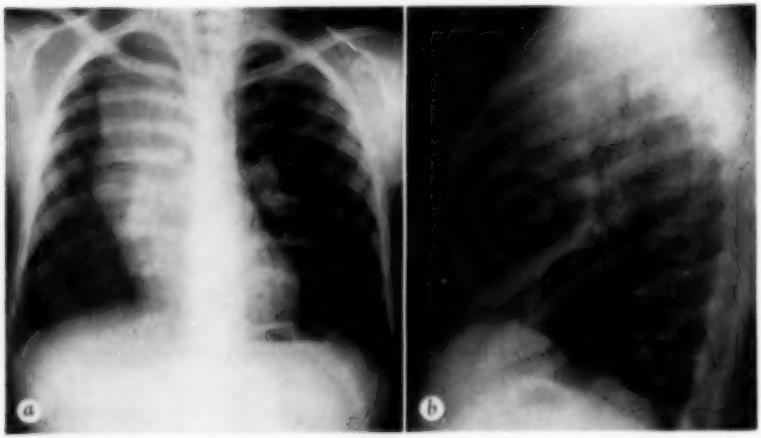

FIG. 7. Thoracic roentgenograms of locally invasive hemangioma of anterior mediastinum in a 13-year-old boy. *a*. Postero-anterior projection. *b*. Lateral projection.

tinal location. This feature is shared by only two other types of primary mediastinal tumor, namely, thymomas and teratomas.

The angiosarcomas resembled the benign tumors in that their borders were well circumscribed on roentgenographic views of the thorax. They tended to be somewhat larger than the benign tumors, and destruction of the anterior portion of the left second rib was present in one case. Because of the infiltrative nature of both of these, it was impossible to remove them completely at the time of operation. Postoperative roentgen-ray therapy was given to one patient. This patient is now hospitalized elsewhere with recurrence of the malignant process 4½ years after operation. The other patient, a 6-year-old girl, died 3 years postoperatively.

One hemangioma and the hemangiopericytoma were completely removed. The other patient with a mediastinal hemangioma, a 13-year-old boy, was found to have a locally invasive tumor (figure 8) precluding complete removal.

Cystic hygromas: Cystic hygromas are comparatively rare lesions, although they are encountered more commonly in infants and children than in adults. They are distinct from coelomic cysts commonly encountered in adults in relation to the pericardial sac. Pathologically, these tumors are made up of masses of dilated lymphatic channels containing clear, watery fluid and lined with flat endothelium.

All 4 patients in this group had a mass palpable in the cervical region on physical examination. One patient complained of dyspnea and one of dysphagia, the remaining 2 being asymptomatic.

The lesion appears roentgenographically as a rather large, unilateral or bilateral mass in the superior mediastinum, usually extending into the neck (figure 9). The margin of the mass is well defined, and the border tends to be straight

FIG. 8. Cut surface of gross specimen which was incompletely removed at operation. Roentgenograms of this patient are pictured in figure 7.

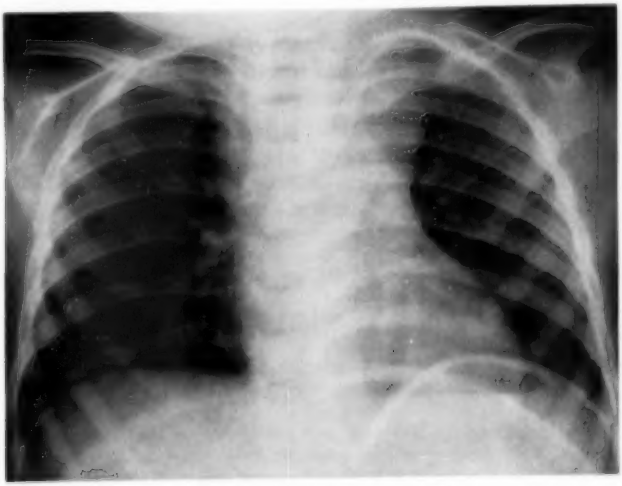

FIG. 9. Postero-anterior thoracic roentgenogram of a $2\frac{1}{2}$ year old girl with cystic hygroma of the mediastinum extending into the neck.

rather than rounded and is directed upward and outward from the level of the hilus of the lung or bifurcation of the trachea to the apex of the thorax.

Complete surgical removal of the lesion is extremely difficult because of adherence of the cyst to the surrounding structures and its extension into the neck. In 2 patients the lesion was completely removed with difficulty at thoracotomy and there has been no recurrence. In 2 other patients biopsy only was done and roentgen-ray therapy was administered postoperatively. In one of these there has been no appreciable change in the size of the mass, but in the other the mass decreased in size by about one half and has since remained unchanged for a period of 10 years.

Grade 4 malignant neoplasm (unclassified): There were four mediastinal tumors that could not be classified histologically. They were considered highly malignant sarcomas of uncertain origin. All four patients were less than 4 years of age and all died of their disease.

In 3 cases surgical exploration was carried out because of a huge mass that practically filled one thoracic cavity. Biopsy was performed in these 3 cases. In the fourth case the tumor was found at the time of post-mortem examination, and it was impossible in this instance also to determine its origin.

SUMMARY

Observations on 58 primary mediastinal cysts and neoplasms in infants and children have been reviewed. Symptoms were present in 35 (60 per cent) of the 58 patients. Symptoms were more commonly associated with teratomatous tumors, enterogenous anomalies, and malignant lesions of all varieties than with any other type of mediastinal lesion.

Neurogenic tumors and teratomatous tumors together represented more than 60 per cent of all of the cases. Vascular lesions and cystic hygromas were observed to occur more frequently in this group of infants and children than in adults. There were no instances of mediastinal goiter, thymoma, or coelomic cyst, in contrast to the findings in adults.

A malignant tumor was present in 14 (24 per cent) of the 58 patients.

SUMARIO

Quistes y Neoplasias Primarios del Mediastino en Lactantes y Niños Mayores

Repásanse aquí las observaciones realizadas en 58 quistes y neoplasias primarios del mediastino en lactantes y niños mayores. Hubo síntomas en 35 (60 por ciento) de los 58 enfermos, hallándose más comúnmente asociados con tumores teratomatosos, anomalías enterógenas y lesiones malignas de todo género que con ninguna otra forma de lesión mediastínica.

Los tumores neurógenos y los teratomatosos juntos representaban más de 60 por ciento del total de casos. Hubo lesiones vasculares e higromas quísticos más frecuentemente en este grupo de lactantes y niños que lo observado en personas adultas. No hubo casos de bocio mediastínico, timoma o quiste celómico, en contraposición a los hallazgos en adultos.

En 14 (24 por ciento) de los 58 enfermos había un tumor maligno.

RESUME

Kystes médiastinaux et néoplasmes primitifs chez des nourrissons et des enfants

Analyse d'observations relatives à 58 cas de kystes médiastinaux et néoplasmes primitifs chez l'enfant et le nourrisson. Des symptômes étaient présents chez 35 d'entre eux (60% des cas) sur 58 malades. Les symptômes étaient le plus fréquemment associés aux embryomes, aux malformations entérogènes et aux lésions malignes de toutes variétés qu'à tout autre type de lésion médiastinale.

Les tumeurs neurogènes et les embryomes représentaient ensemble plus de 60% de la totalité des cas. L'incidence des lésions vasculaires et les hygromas kystiques était plus fréquente dans ce groupe de nourrissons et d'enfants que chez l'adulte. Il n'y a eu aucun cas de goître médiastinal, thymome ou kyste coelomique, à l'encontre des découvertes faites chez l'adulte.

Une tumeur maligne était présente dans 14 cas (24%) sur 58 malades.

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DIAGNOSTIC THORACOTOMY IN THE STUDY OF "IDIOPATHIC" PLEURAL EFFUSION[1,2]

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INTRODUCTION

Thorough clinical study of the patient and laboratory examination of the pleural fluid usually lead to an etiologic diagnosis in cases of pleural effusion. There remains a group of patients in whom these methods of study fail to explain the reason for the accumulation of fluid in the pleural space. In some of these cases thoracotomy with pleural biopsy is capable of providing a definitive diagnosis.

It has long been held that "idiopathic" pleural effusion usually is of tuberculous origin, especially in young patients. Yet, just as there is some truth in this contention, there are also some exceptions to it. Hence, in view of the methods of diagnosis now available, it seems unwise, in many such instances, to burden the patient with the stigma, expense, and inconvenience of antituberculous therapy when proof of such infection has not been established. Moreover, the advisability of early diagnosis of other causes of pleural effusion attracts no serious argument.

In 1955, Stead, Eichenholz, and Stauss (1) reported their experiences with pleural exploration in 24 patients who had pleural effusion of undetermined cause. The ages of these patients ranged from twenty to fifty-six years and, because of positive reactions to tuberculin and other findings, all were suspected of having tuberculosis. Even in this selected group, 9 of the 24 patients at thoracotomy were found to have no evidence of pulmonary or pleural tuberculosis. In 7 of these patients the final diagnosis was pleural inflammation of other cause; in one, thoracic trauma; and in one, pleural fluid and thickening caused by spontaneous pneumothorax.

In 1954, Sutliff, Hughes, and Rice (2) reported the results of pleural biopsy in 21 patients who had pleural lesions which persisted after absorption or removal of the pleural fluid. By this method of diagnosis, 17 were found to have tuberculosis, 3 were seen to have carcinoma, and one was found to have blastomycosis.

MATERIAL

The ages of the group of 21 patients herein reported ranged from twenty-six to sixty-nine years; the average age was fifty-three years, indicating that these patients were in the age group in which pleural lesions other than tuberculosis occur with significant frequency. One or more symptoms compatible with pleural disease were reported by all: dyspnea, sensation of heaviness in the chest, chills, fever, or homolateral thoracic pain.

[1] From the Mayo Clinic and the Mayo Foundation (part of the Graduate School of the University of Minnesota), Rochester, Minnesota.

[2] Presented before the Medical Session, as part of *Section 6B*, at the annual meeting of the National Tuberculosis Association, New York, New York, May 23, 1956.

The duration of symptoms attributable to pleural disease ranged from two weeks to three years, the average being seven months. In all cases clinical examination failed to identify the local or systemic disease to which the pleural effusion could be attributed. In 19, pleural fluid was aspirated, often repeatedly, either for laboratory examination or for relief of symptoms, or both. In the other 2 cases attempts at thoracentesis yielded no fluid, despite roentgenographic evidences that fluid was probably present. The results of laboratory examination of the aspirated fluid will be outlined below.

RESULTS

In table 1 are listed the diagnoses established by pleural biopsy in this series of cases.

In the single case classified as "trauma," it is interesting that there was no history of injury. The patient was a man fifty-two years old who had had slight pain in the lower part of the right thorax for ten days. Thoracentesis yielded 200 ml. of bloody fluid, examination of which gave negative bacteriologic and cytologic results. Thoracotomy revealed a large rent in the right side of the diaphragm, with herniation of the liver and omentum into the thorax. After repair of the defect, the convalescence of the patient was uneventful, and there was no further accumulation of fluid.

In the 6 cases of neoplasm, six different types of tumor were encountered, as indicated in table 2. The first was found to be a large, cellular fibroma situated in the vertebral gutter; the patient had undergone thoracentesis five times, each yielding an average of 1,500 ml. of bloody fluid. The patient found to have a pleural mesothelioma had roentgenographic evidence of lobulated pleural lesions which suggested either tumor or loculations of fluid. The patient with lymphosarcoma had effusion of fluid bilaterally; thoracentesis had been per-

TABLE 1

DIAGNOSES ESTABLISHED BY THORACOTOMY IN 21 CASES OF IDIOPATHIC PLEURAL EFFUSION

Trauma	1
Neoplasm	6
Tuberculosis	5
Other inflammatory processes	7
Indeterminate	2
Total	21

TABLE 2

TYPES OF NEOPLASM IN 6 CASES OF THORACOTOMY DONE TO ESTABLISH CAUSE OF PLEURAL EFFUSION

Fibroma	1
Mesothelioma	1
Lymphosarcoma	1
Adenocarcinoma	1
Undifferentiated metastatic carcinoma	1
Metastatic melanoma	1
Total	6

formed five times, on each occasion yielding 1 to 2 liters of blood-tinged fluid which, on cytologic examination, was found to contain many lymphocytes. The patient with adenocarcinoma (primary site not determined) had undergone thoracentesis thirty times, each yielding 3 or more liters of amber fluid. Cytologic examination of fluid was not available at that time (1941). Of the other 2 patients with neoplasm, one had an undifferentiated metastatic carcinoma (primary site not determined) and the other had a metastatic melanoma (an eye had been removed at another hospital twelve years earlier); in both cases cytologic examination of the pleural fluid gave negative results.

Five of the patients were found to have pleural nodules of caseous granuloma; bacteriologic study of the excised lesions revealed human tubercle bacilli. Although the diagnosis of tuberculosis was proved also by the subsequent growth of tubercle bacilli from the pleural fluid in all of these cases, thoracotomy was performed in an attempt at early diagnosis. Malignancy was suspected, since all these patients were men forty-nine to sixty-nine years old.

In table 3 are listed the types of inflammatory processes encountered in the 7 patients who had inflammatory diseases other than tuberculosis. Despite thorough bacteriologic study of the pleural fluid and excised tissue, no causative organism could be identified in any of this group. One patient had multiple small nodules on the surface of the right upper lobe, microscopically seen to be healed granulomas. Two had marked fibrinous pleuritis; 3 had a thick hyaline or fibrous peel covering all or part of the lung, requiring decortication. In one patient in whom there was a thick pleural peel, the pleural fluid (thoracentesis done seven times) was grossly bloody.

Of these 5 patients with fibrinous or fibrous pleuritis, only 2 gave histories of antecedent infection to which the pleuritis could be related reasonably: one had been told three years earlier that she had an abscess of the lung, and the other reported having had chills and fever four months earlier. In the absence of more specific information as to pathogenesis, the inclination is to regard the fibrinous pleuritis and the fibrous peel as different stages of the same process, possibly with peripheral pneumonitis as the antecedent lesion.

One of the patients in the group with nontuberculous inflammatory processes had active rheumatoid arthritis. The pleural fluid was serous and contained many clots of fibrin. Both the pleura and the pericardium were thick and edematous and showed highly vascular inflammatory changes. Results of bacteriologic study of both fluid and surgical specimens of tissue were negative, suggesting

TABLE 3

"OTHER INFLAMMATORY PROCESSES" IN 7 CASES OF THORACOTOMY DONE TO ESTABLISH CAUSE OF PLEURAL EFFUSION

Healed granuloma	1
Fibrinous pleuritis	2
Fibrous peel	3
Rheumatoid pleuritis	1
Total	7

an etiologic relationship between the inflammatory process in the joints and pleura.

Of the 2 patients whose condition was classified as indeterminate (table 1), one, a man twenty-six years old, had had chills, fever, and pleuritic pain for a month. The pleural space contained 2 liters of bloody fluid, but examination of the lung and pleura revealed no other evidence of disease; recovery was uneventful and there was no further accumulation of fluid. The other patient, a man forty-seven years old, had had pleuritic pain for ten days; surgical exploration of the pleural space showed only clotted blood and organizing fibrin, and afforded no clue to the basic disease process.

SUMMARY

An account is presented of 21 patients for whom surgical examination of the pleura was done and from whom specimens for biopsy were taken in attempts to establish the cause of pleural effusion. The diagnoses established were as follows: trauma in one patient, neoplasm in 6, tuberculosis in 5, other inflammatory processes in 7, and indeterminate disease in 2 patients. The procedure gave valuable aid in diagnosis as well as in prognosis and in the selection of suitable therapy.

SUMARIO

La Toracotomía Diagnóstica en el Estudio del Derrame Pleural "Idiopático"

Preséntase una reseña de 21 enfermos en quienes se ejecutó el examen quirúrgico de la pleura y de los que se obtuvieron ejemplares para biopsia tratando de establecer la causa del derrame pleural presente. Los diagnósticos establecidos fueron éstos: traumatismo en un enfermo, neoplasias en 6 enfermos, tuberculosis en 5, otros procesos inflamatorios en 7 y enfermedad indeterminada en 2. El procedimiento proporcionó valiosa ayuda en el diagnóstico así como en el pronóstico y en la selección de la terapéutica apropiada.

RESUME

Thoracotomie diagnostique dans l'étude de l'épanchement pleural "idiopathique"

Présentation d'un compte-rendu concernant 21 malades chez lesquels il a été fait un examen de la plèvre avec prélèvement biopsique pour essayer d'établir la cause de l'épanchement pleural. Les diagnostics établis furent les suivants: traumatisme chez 1 malade, néoplasie chez 6, tuberculose chez 5, divers processus inflammatoires chez 7 et lésions indéterminées chez 2. Ce procédé constitue une aide de valeur à l'égard du diagnostic comme du pronostic et pour la sélection d'un traitement adéquat.

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Addendum

Since preparation of the manuscript, the following additional pertinent references have come to the writers' attention:

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Heller, P., *et al.*: New England J. Med., 1956, *255*, 684.

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Notes

A SIMPLE TECHNIQUE FOR THE DIFFERENTIATION OF TUBERCLE BACILLI AND SAPROPHYTIC MYCOBACTERIA

Presumably because of improved standards in the treatment of tuberculosis in recent years, there has been a gradual decrease of cultures of tubercle bacilli obtained from the various clinical specimens which are regularly sent to the tuberculosis department of this institute. The decrease does not only show in the relative number of cultures positive for tubercle bacilli but is also evident from the lower "degree of positivity," i.e., the number of colonies per tube, which indicates that most specimens contain only a very small number of tubercle bacilli, if any.

Simultaneously with this development, it has been observed that there has been a proportional increase of false "positive" cultures due to the growth of saprophytic or commensal or doubtfully pathogenic mycobacteria. As several strains were found closely resembling *M. tuberculosis*, especially the bovine type, an attempt has been made to find methods for differentiating saprophytes from strict parasites. Since the introduction of isoniazid, guinea pig inoculation is no longer a reliable means of differentiation, as isoniazid-resistant strains may erroneously be taken for saprophytes, owing to their attenuated pathogenic properties.

Several methods of differentiation have been tried, including Dubos' and Middlebrook's neutral red test,[1] the ability to proliferate on simple media, such as glucose-broth agar, or in the presence of 10 γ of PAS per ml.[2] In this laboratory these methods were unsatisfactory in so far as some strains were encountered that showed an atypical reaction with one or more of these methods.

In the experience of the writers, the combined test which is described below was more reliable.

Three tubes of Löwenstein (modified Jensen-Bekker) medium (I, II, and III) were used, one of which (III) contained isoniazid in a concentration of 10 γ per ml. Material from primary isolates of acid-fast bacilli which are suspected[3] of being atypical is transferred to these tubes in a thin central inoculation track. Tubes I and III are incubated at 37°C. for three weeks, and tube II for the same period at 24°C.

Growth occurring at 37°C. (tube I), in combination with the absence of growth at 24°C. (tube II), and on the medium containing isoniazid (tube III), is highly indicative of the presence of *M. tuberculosis*. Growth at 24°C. (tube II) is characteristic of the presence of a saprophytic strain. If, on the other hand, proliferation occurs in the presence of isoniazid (in tube III), either a tubercle bacillus of the isoniazid-resistant type or a primary resistant saprophytic species may be present. To decide between these possibilities a catalase test according to Middlebrook[4] is applied with a mixture of equal parts of 30

[1] Dubos, R. J., and Middlebrook, G.: Am. Rev. Tuberc., 1948, *58*, 698.

[2] Penso, G.: In *Bacilles Tuberculeux et Paratuberculeux*, Masson et Cie., Paris, 1950, p. 106.

[3] Characteristics which arouse such suspicion are: the presence of only one or a small number of not entirely typical colonies, cultures which on smear show bacilli distributed more or less evenly over the slide, absence of cord factor, pigmentation, et cetera.

[4] Middlebrook, G.: Am. Rev. Tuberc., 1954, *69*, 471.

TABLE 1

RESULTS OF TEST OF 1,735 CULTURES ISOLATED FROM 25,000 CLINICAL SPECIMENS

Tube I Growth at 37°C.	Tube II Growth at 24°C.	Tube III Behavior on Media Containing Isoniazid		Interpretation	Number of Strains
		Growth	Catalase Reaction		
Growth	No growth	No growth		*M. tuberculosis*	1,527
Growth	No growth	Growth	Negative	*M. tuberculosis*	132
Growth	No growth	Growth	Positive	Saprophyte	13
Growth	Growth	Growth	Positive	Saprophyte	60
Growth	Growth	No growth		Saprophyte	3

per cent hydrogen dioxide and 10 per cent Tween® 80 in water. In this test saprophytic mycobacteria are easily recognized by their prompt and abundant production of foam, whereas pure cultures of tubercle bacilli resistant to 10 γ of isoniazid per ml. are invariably[5] found to be catalase negative. In addition, a few saprophytic strains were encountered that were only moderately catalase positive; these were all able to grow at 24°C.

It is important to note that the catalase test should only be carried out with the culture on a solid medium containing 10 γ of isoniazid per ml. A medium without this substance allows the proliferation of tubercle bacilli of normal drug susceptibility which are catalase positive. That this point should not be overlooked follows from other experiments in which 57 of 119 fresh isolates from isoniazid-treated patients were found by one of the present writers to contain, on primary isolation on Löwenstein medium (without isoniazid), a mixture of catalase-positive and catalase-negative bacilli.

Up to the present time, 1,735 Ziehl-Neelsen positive cultures isolated from approximately 25,000 clinical specimens have been investigated, including also the directly recognizable strains of tubercle bacilli for comparison. The results of the test are shown in table 1.

It may be seen in the table that 1,527 strains responded to the tests in a way which is considered typical of normal tubercle bacilli. The pathogenicity of 180 of these strains was ascertained by injection into guinea pigs, as a result of which 178 contracted a generalized tuberculosis. The two remaining strains appeared to be of attenuated virulence, comparable with the BCG type.

As none of the 132 isoniazid-resistant and catalase-negative strains exhibited any growth at 24°C. and, because of the typical appearance on a normal Löwenstein slope, they may also be regarded as tubercle bacilli.

Among the cultures, 76 were saprophytic strains, since they either were able to grow at 24°C. or were isoniazid resistant and catalase positive. In the long run, many of the strains were able to produce a bright yellow or orange pigment, although in an earlier phase of growth in preponderance they might easily have been taken for bovine tubercle bacilli. Of the 76 strains of saprophytic mycobacteria, 73 were isoniazid resistant and catalase positive, while only 63 were capable of visible growth at 24°C. within three weeks. Consequently, examining the capability of growth on a medium containing isoniazid, followed by a catalase test, is a better method to distinguish saprophytic or commensal mycobacteria from tubercle bacilli than the growth experiment at 24°C. solely, although the best results are obtained with the combined test.

[5] MARSEILLE, A.: Nederl. tijdschr. v. geneesk., 1955, *99*, 619.

Apart from the 76 saprophytic strains isolated in the present investigation, there was a collection of 145 strains of acid-fast saprophytes that had been isolated previously; their nonpathogenicity had been confirmed by injection into guinea pigs. These strains appeared to be invariably isoniazid resistant and catalase positive.

As the method described for the differentiation of tubercle bacilli and acid-fast saprophytes is relatively simple, requires less time than the traditional guinea pig method, and is also reliable for isoniazid-resistant strains, the guinea pig method is seldom employed in this laboratory at the present time.

In summary: Acid-fast saprophytes are easily differentiated from tubercle bacilli by a paired growth test, made both at 24°C. and on a Löwenstein slope containing 10 γ of isoniazid per ml. maintained at 37°C. Both cultures are incubated for three weeks. A strain is considered to be not a genuine tubercle bacillus if multiplication occurs at 24°C. or if growth occurs on the medium containing isoniazid, provided that the latter growth is found to be catalase positive.

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LENGTH OF STAY AND CRITERIA FOR DISCHARGE IN A LARGE TUBERCULOSIS CENTER

The era of chemotherapy for tuberculosis has brought numerous changes in the management of this disease. The writer is frequently asked the following questions:

What are your criteria for the so-called early discharge of patients who will continue chemotherapy on an outpatient basis?

What is the length of stay in the Sanitarium of patients who receive the early discharge?

This report is intended to provide answers to these questions.

The Municipal Tuberculosis Sanitarium contains 1,452 beds for tuberculous patients and also operates six outpatient clinics distributed throughout the city of Chicago. Until the end of 1952, patients were advised to remain in the Sanitarium until their disease could be classified as inactive, and there was no program for post-sanatorium chemotherapy. This resulted in huge waiting lists of patients unable to obtain beds in order to receive tuberculosis treatment. Early in 1953, the policy was changed so that patients under certain conditions could obtain early discharge and continue their chemotherapy on an outpatient basis. This program has been eminently successful over the past three years. Patients are able to obtain prompt admission to the Sanitarium. The number admitted annually has increased by 50 per cent and the number of patients obtaining chemotherapy at any one time has tripled.

Written criteria for discharge are important, both in orienting a large medical staff and in the indoctrination of patients. Prior to discharge, each case is reviewed by a conference of physicians and representatives of the social service and rehabilitation staffs. The following is an outline of all classes of discharge at the Municipal Tuberculosis Sanitarium:

Class A: Discharged as "Inactive": the patient's disease must fulfill the criteria of the 1950 National Tuberculosis Association classification for inactive disease.

Class B: Discharged with permission:

1. Discharged as "Arrested": the patient's tuberculosis must fulfill the applicable 1950 National Tuberculosis Association criteria; the patient must have suitable living quarters and must not live with infants less than two years of age. ("Arrested" classification has been discontinued in the 1955 National Tuberculosis Association *Diagnostic Standards*.)
2. Discharged as "Active Improved Without Cavity": the patient should be essentially asymptomatic, roentgenograms should show marked improvement (no demonstrable cavitation, and at least 50 per cent clearing of infiltration), at least three consecutive 24-hour sputum concentrations should be negative for tubercle bacilli, prognosis should be good, living quarters suitable, with no infants less than two years of age in contact.
3. Discharged as "Post-Surgical with Good Prognosis": patients who have had major chest surgery, and who fail to qualify under *Class A* or *Class B 1*, should be discharged as *Class B 3* if they can fulfill approximately the same requirements as in *B 2*.
4. Discharged with "Maximum Hospital Benefit" ("open-negative" group): patients unable to fulfill the cavity closure requirement in *Class B 2* may be discharged in this class. They should be essentially asymptomatic; have stable roentgenograms for at least three months; have at least three consecutive 24-hour sputum concentrations which are negative for tubercle bacilli; should have suitable living quarters; and should not be in contact with children or adolescents.
5. Transferred to another institution, or leaving the city: patients are discharged in this

category if there is suitable evidence that they are entering another institution or leaving Chicago.

Class C: Patients may leave "against medical advice" by notifying the hospital at least 48 hours in advance and after an interview with their physician.

Class D: Patients who leave without notice.

Class E: Patients may be discharged by the executive staff for gross and deliberate infraction of the hospital rules; in this event they are classified as disciplinary discharges.

Class F: Died.

Class G: Patients who were admitted for a short term for a special procedure or test (wax pack removal, pulmonary function test, et cetera).

Closure of cavities for *Class B 2* discharge should be verified, if indicated, by use of special roentgenography, such as lordotic views or laminagrams.

For *Class B 1*, *B 2*, *B 3*, and *B 4* discharges, the patient's sputum must be consistently negative for acid-fast bacilli on microscopy but need not be negative for tubercle bacilli on culture. In most of these patients, the sputum is, in fact, negative on culture also, but this is not a requirement for discharge because of the delay which would ensue while waiting for culture reports.

Post-surgical discharges (*Class B 3*) are usually given three to six months following surgery, providing the remaining lung areas fulfill the requirements of *Class B 2*.

Maximum hospital benefit (*Class B 4*) discharges are conferred on patients who have achieved stability of lesions after prolonged chemotherapy but who have failed to close all cavities. They may be patients who refuse surgery or are unsuitable for surgical procedure because of too extensive disease or associated diseases.

In table 1 may be seen the average length of stay of the patients in 1955 according to the various types of discharge. The unsanctioned discharges are combined (*Classes C*, *D*, and *E*) and are associated with the shortest hospital stay (150 days). The "early discharge" groups (*Class B 2*, *B 3*, and *B 4*) vary in duration of hospitalization from 262 to 433 days. Of 986 patients who were discharged alive with consent (*Classes A* to *B 4*), 692 patients received such early discharge.

The average stay for all patients in 1952 (before outpatient chemotherapy) was 434 days. In 1955, the average stay was 300 days. The median stay was 218 days in 1955. This figure indicates that half the patients stayed more than 218 days and half stayed less, and

TABLE 1

MUNICIPAL TUBERCULOSIS SANITARIUM, 1,150 BEDS
AND
NORTH RIVERSIDE BRANCH FOR MEN, 212 BEDS
Patients Discharged, Year 1955

Type of Discharge	Women	Average Days	Men	Average Days	Total	Average Days
A—Inactive	67	366	113	524	180	465
B 1—Arrested	73	456	41	424	114	445
B 2—Active—no cavity	100	281	68	232	177	262
B 3—Post-surgical	106	479	43	320	149	433
B 4—Maximum hospital benefit	82	517	284	388	366	417
B 5—Transferred	12	600	19	344	31	443
C, D, & E—Irregular	219	146	381	152	600	150
F—Expired	35	379	90	317	125	334
G—Short term	48	53	42	75	90	63
Total discharged	751	315	1,081	289	1,832	300

is probably a more accurate measure than the average stay. Any method of determining duration of hospitalization by considering all of the patients together is poor. It is distorted by the short-stay unsanctioned discharges at one end and by the long-stay incurables at the other. Dividing the patients into groups, therefore, gives a clearer picture.

* * *

Early discharge of selected patients has proved to be extremely helpful in eliminating long waiting lists for sanatorium care. Hospital admissions increased 50 per cent as a result of this program. Another benefit was the drop in the irregular discharge rate from 57 to 34 per cent. It is apparent that hope of early discharge encourages patients to remain in the hospital until they receive permission to leave.

Experience with 5,400 outpatients receiving chemotherapy during the past three years has given assurance that the criteria for discharge are safe. The relapse rate as previously reported[1] has remained very low.

The "active–no cavity" (*Class B 2*) group, discharged in an average of 262 days, consisted of patients making an uneventful recovery. Post-sanatorium chemotherapy is continued until three to six months after the patient's tuberculosis can be classified as "inactive." The patient is told to return to work when he is so classified. The relapse rate in this group has been approximately 1 per cent in the first year after leaving the hospital.

The "maximum hospital benefit" (*Class B 4*) group was discharged in an average of 417 days. This group comprised the so-called "open-negative" patients with residual cavitation who either refused or were not suitable for surgery. Many were elderly men. The relapse rate in this group has been approximately 5 per cent in the first year after discharge. Post-sanatorium chemotherapy is continued indefinitely in this group unless the cavities close. Because the patients are under continuous observation in the outpatient clinics, relapse is detected promptly and rehospitalization is carried out. Observation of contacts has revealed no evidence that these patients have spread infection.

Careful review of each case prior to discharge is helpful in properly classifying the patient for the guidance of physicians in the outpatient department. The criteria are sufficiently flexible to allow the staff full latitude of judgment and the patient a limited degree of choice concerning the time of discharge.

Cooperation in taking post-sanatorium chemotherapy is excellent in the groups of patients who receive an early discharge. This is in sharp contrast to former experience with pre-sanatorium chemotherapy patients.

The value of the program in making prompt hospitalization possible and in tripling the number of patients receiving chemotherapy can hardly be overestimated.

In summary: The City of Chicago Municipal Tuberculosis Sanitarium, because of a very long waiting list in 1953, started a program of early discharge of selected patients who would receive post-sanatorium chemotherapy. The criteria for discharge and the duration of stay for each group are given. The program resulted in prompt admission of all applicants for sanatorium care, a 50 per cent increase in annual admissions, a marked decrease in the irregular discharge rate, and a twofold increase in the number of patients receiving chemotherapy (in hospital plus clinics) at any one time. This was accomplished with essentially the same facilities, personnel, and budget.

City of Chicago Municipal Tuberculosis Sanitarium
Chicago, Illinois

Meyer R. Lichtenstein

June 12, 1956

[1] Lichtenstein, M. R.: Nat. Tubere. A. Tr., 1954, p. 301.

THE USE OF THE MADISON SENTENCE COMPLETION FORM IN A SMALL TUBERCULOSIS SANATORIUM[1]

The Madison Sentence Completion Form has been in use in a number of tuberculosis hospitals.[2, 3] The form is a psychologic test designed to detect harmful attitudes among tuberculous patients which may seriously interfere with treatment. A prognostic scale, based on the patient's sentence completion responses, has been of considerable aid in predicting the likelihood of a patient's leaving the hospital against his doctor's advice.[4] The test has also been employed as a means of polling patients' attitudes toward various hospital services and activities.

The form has been of most value in large tuberculosis hospitals, particularly those employing a psychologist. The aim of this study was to determine whether the test could be used as effectively in a small tuberculosis sanatorium which does not have a staff psychologist or other staff members especially trained in the measurement and evaluation of patients' attitudes. This investigation was further designed to answer such questions as: Who among the staff personnel would be best qualified to administer the form? How can the form best be utilized in the hospital? Should the form be administered routinely to all patients or should it be used upon referral only for specific problem patients? Finally, how would the staff in a small sanatorium react to this type of attitude questionnaire? If the results of the study were favorable, it was hoped that the use of the form would spread to other small tuberculosis institutions.

The site chosen for the study was Lake View Sanatorium, Dane County Tuberculosis Hospital, just outside of Madison, Wisconsin. Lake View was thought to be fairly typical of small tuberculosis sanatoriums. Its average patient population is approximately 90, with an equal proportion of male and female patients. The professional staff consists of two doctors, thirteen registered nurses, a medical social worker, and an occupational therapist. In addition, the hospital employes the services of a consulting psychiatrist twice a month.

During the initial phase of this investigation, approximately one-half of the patient population was seen by one of the present writers. Each of these patients received an individual, verbal administration of the form. The test results were discussed at weekly staff conferences in order to familiarize the staff with the form and its uses. Summaries of the patients' expressed attitudes toward the medical treatment, toward specific hospital services, expressions of feeling about the hospital meals, specific ward complaints, and suggestions for improvement in hospital living were turned over to the appropriate staff members, i.e., the list of responses revealing the patients' attitudes toward hospital meals were presented to the dietician, et cetera.

The occupational therapist, the medical social worker, and three nurses (including the Patient Educator) then were invited to participate in the testing program. This was done in an attempt to evaluate the effectiveness of the form when administered and interpreted by staff personnel who had relatively little formal training in test administration. These five staff members were given brief instructions on the scoring and analysis of the patients' test responses, after which they each administered the test to two different patients. They also were asked to describe their impressions of their testing experiences.

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[1] This study was supported by a research grant from the Madison Tuberculosis Association, Madison, Wisconsin.

[2] Calden, G.: Am. Rev. Tuberc., 1953, *67*, 722.

[3] Hiddlestone, H. J. H.: J. Brit. Tubere. A., 1954, *35*, 223.

[4] Calden, G., *et al.*: Am. Rev. Tubere., 1956, *73*, 338.

The testers stated that they encountered very little difficulty in scoring and analyzing the test results. Their written test reports, based on a standard outline for writing up the Madison Sentence Completion Form, were examined by one of the writers, and each report was found to be highly satisfactory. In considering who among them were best qualified to do the testing, the impression was gained that very few differences were evident among the various professional groups. Furthermore, it was believed that the interest and motivation of the tester was a more important consideration in the selection of a qualified person than whether the tester was a nurse, social worker, or rehabilitation therapist. This suggests that any professional staff member who is sufficiently interested in using the Madison Sentence Completion Form is potentially qualified to administer and interpret the test's results.

Toward the end of the study, the entire staff was asked to fill out an evaluation form expressing their feelings about the testing program and their appraisal of its value in a small tuberculosis sanatorium.

An analysis of the staff's evaluations revealed that almost everyone believed that the testing had served some useful purpose with individual patients. In other words, it was generally agreed that the test reports frequently revealed aspects of the patient's attitudes which they hadn't previously known. Approximately 90 per cent of the personnel polled thought that the study had been worth while because it had stimulated considerable staff interest and discussion. They believed that the new information they obtained could be used to make patients more contented and to point up some irregular discharge risks who might be salvaged by appropriate action. The systematic appraisal of attitudes also "convinced some of the staff that patients are human." Others believed that the test results merely confirmed staff opinions about patients and that nothing could be gained by predicting irregular risks because "you can't keep patients in a san." Approximately 80 per cent of those polled thought that the survey of patients' attitudes toward specific hospital activities was very informative. It was maintained that surveys of this kind, when done periodically, can provide the staff with a good index of patient morale. Such "public opinion polls" tend to point up the strong as well as the weak points at the sanatorium and permit revisions in hospital procedures.

In general, the staff believed that, although the form was helpful in many ways, its value would be greatest in a small sanatorium that had a markedly discontented patient population or that had an unusually high irregular discharge rate, or in an institution where there was little opportunity for understanding or becoming well acquainted with patients through regular hospital contacts. However, the majority of staff members agreed that in a well-staffed sanatorium, such as Lake View, where patient and staff morale was relatively high, and the irregular discharge rate was relatively low, the value of the form was not sufficient to justify the staff time necessary for its continued use on a routine basis.

The staff members were divided in their opinion of what would be the best testing procedure to follow in a small sanatorium that would adopt the form. Half of the personnel polled were of the opinion that it would be best to distribute the form to all patients in order to obtain an adequate public opinion survey. The remaining half thought that it would be more advisable to test only problem patients on an individual basis in order to familiarize the staff with their particular complaints and adjustment problems. The factors of time and availability of personnel for the testing program were important considerations in determining how extensively the form should be utilized.

One of the interesting by-products of this study was the opportunity it gave for appraising the differences in attitudes of tuberculous patients in a large and in a small

sanatorium. In a recent letter to the Editor of this journal, Day[5] has pointed out that such differences in patients' responses to hospitalization may account for "smaller establishments showing the better records than larger ones" in regard to irregular discharge. This difference in the percentage of patients who leave prematurely is readily observed in this geographic area, since Lake View's irregular discharge rate averages about 13 per cent, whereas the larger Veterans Administration Hospital in Madison, Wisconsin (with a population of more than 300 tuberculous patients) has an average irregular discharge rate between 30 and 40 per cent.

A comparison of the sentence completion test responses of patients of both hospitals suggests that the differences in irregular discharge may be significantly correlated with differences in the degree of contentment with hospitalization expressed by the two groups of patients. In general, the expressed attitudes of the Lake View patients tended to be more of the "everything is fine and I have no complaints" variety. For example, when asked to indicate what they disliked most about hospitalization, a comparison of two randomly selected groups of test records from both hospitals yielded the following results:

a. Dislikes concerning long stay and confinement:
Lake View 25%
Veterans Administration Hospital 25%
b. Complaints about specific hospital activities:
Lake View 32%
Veterans Administration Hospital 71%
c. Have no complaints:
Lake View 43%
Veterans Administration Hospital 4%

Comparisons of attitudes toward staff personnel and specific ward activities showed similar results, reflecting the more accepting and less critical reactions among patients in the smaller sanatorium.

* * *

Assuming that these disparities in the feelings and adjustments of patients do exist, it would certainly be important and valuable to attempt to ascertain the reasons for this. Several speculations are herewith offered. The writers have had contact with both installations, and several differences seem apparent. The most marked is a difference in, for lack of a better term, "atmosphere." Friendliness and informality seem to pervade Lake View. Each staff member is familiar with and experiences daily contact with each patient. Also, the personnel turnover is less. Rules are necessary here, as in any hospital, but there is a degree of flexibility which is not usually possible in a larger hospital where efficient functioning seems to depend in a large part upon more rigid adherence to formal rules and procedures. Here at Lake View, it seems to the writers, the patient retains a greater feeling of individuality, instead of considering himself as just an unnoticed member of a huge patient population. It is assumed that the patients receive more individual attention and thus feel more "at home." Patients are allowed greater freedom in the keeping of personal possessions in their rooms, and this, too, would tend to make them feel more "at home." As a result, it seems to the writers, that the patients at this small sanatorium are actualy happier and better adjusted to confinement and long hospitalization.

It is also believed that there is a difference in types of people at the two institutions under consideration. A greater proportion of the Veterans Administration Hospital

[5] Day, G.: Am. Rev. Tubere., 1956, *73*, 597.

population is made up of "hardened" veterans of tuberculosis, consisting of those who have been at several other hospitals, who have a long record of previous irregular discharges, and who are as much unsettled in their personal lives as they are in the hospital setting. The patients in the Veterans Administration Hospital also are a relatively heterogeneous group coming from different walks of life and various geographic areas, having markedly divergent racial and cultural backgrounds, and demonstrating a wide assortment of personal attitudes and interests. One need only observe the striking dissimilarities in food tastes among individual patients in order to convince oneself of the mixed character of the patient population of the Veterans Administration Hospital. This disparity of backgrounds and attitudes makes it more difficult to cater to the needs of individual patients. It also makes it more difficult to foster a group spirit and group identification with the hospital —factors which are highly essential in diminishing dissatisfaction among patients. The Lake View patient population, on the other hand, consists largely of rural county people whose main concern is getting cured and who are willing to undergo a full and complete cure. They seem to be a more settled and homogeneous lot who have a greater communality of interest and background and are less critical of the care and treatment they are receiving.

Whatever the reasons, it is quite apparent that differences do exist in these two patient populations. Patients at Lake View do have fewer complaints, less unrest, and fewer problems of adjustment. As a result, the Madison Sentence Completion Form is less valuable in this setting. The test would be of some value with "problem" cases and as a periodic attitude survey regarding hospital services. This would involve a minimum of staff time and would seem to be of sufficient value to warrant consideration. If used for this purpose, it can be administered, scored, and written up by any of the various professional personnel usually employed in a small sanatorium. It would be valuable in larger sanatoriums and in sanatoriums where contact between patients and staff and inter-staff contact leaves something to be desired.

In summary: In contrast to its value in a large tuberculosis hospital, the Madison Sentence Completion Form seems less useful in a small tuberculosis sanatorium where patient adjustment is good and the percentage of irregular discharges is small. It is believed that actual differences in types of patients, as well as differences in the two types of hospitals, might explain, in part, the reduced value of the test at the smaller institution. The most feasible plan for small sanatoriums to follow, in the light of these results, would appear to be the use of the test on "problem" cases and as a periodic "public opinion poll" of patients' attitudes. Any one of the various professional staff members is potentially capable of administering and interpreting the form, given some instruction in its use.

Veterans Administration Hospital
Madison, Wisconsin
and
Lake View Sanatorium
Madison, Wisconsin

William C. Lewis
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June 22, 1956

EFFECT OF DRUG THERAPY UPON THE SURVIVAL OF TUBERCULOUS PATIENTS

The effect of the antimicrobial drugs streptomycin, para-aminosalicylic acid (PAS), and isoniazid in prolonging the lives of tuberculous patients is so obvious as to need little discussion, but their actual value, in quantitative terms, requires further study. Such a study may permit a comparison of the rate of survival of patients who receive drug treatment with patients who do not receive drugs, as well as with patients treated with therapeutic agents which may be developed in the future. It is the purpose of this paper to compare the survival of patients receiving antituberculous chemotherapy with a similar group not receiving drugs.

In a previous paper,[1] data were presented regarding the survival from tuberculosis of mental patients during the period between 1941 and 1949. During most of this period antimicrobial therapy was not available, and even during the last two or three years of this period drugs were used to a very small extent. Beginning about 1950, however, steadily increasing amounts of these drugs became available, so that soon there was a sufficient supply for all patients considered eligible for this type of therapy. The survival rates for the five years following the diagnosis of tuberculosis in the first group of patients (untreated) were compared with the survival rates in the second group ("treated") upon the premise that differences in rates were due to the effect of the therapeutic agents used.

A group of 981 patients who developed tuberculosis while in the hospitals of the New York State Department of Mental Hygiene between 1950 and 1954 were used in this study. The maximal period of observation was five years; the minimal, one year. Although no information has been obtained for each patient regarding the use or non-use of antimicrobial therapy, since the use of these drugs was widespread during most of the five years of this study period, a large proportion of the patients received at least some drug therapy. Inasmuch as the earlier group was studied prior to any considerable use of chemotherapeutic drugs and the two groups are quite similar in other respects, any differences in survival are attributed to the medication used.

The distribution of these patients by age, sex, mental diagnosis, and stage of disease was not materially different in this group of patients from that included in the earlier study.

Streptomycin, PAS, and isoniazid were all used in various combinations and in the usual dosages. Thoracic surgery and pneumoperitoneum were used to a limited extent during both periods. The use of pneumothorax has decreased during the past few years. The hospital routine regarding bed rest, diet, and general care of patients was unchanged during the two periods.

Since all of the patients in this study developed tuberculosis during their stay in the mental hospitals, they are compared with the group called "new" cases in the previous paper, i.e., the group of patients who developed tuberculosis while under observation, so that the approximate duration of the tuberculous disease was known.

The life-table method was used in the preparation of the tables for this report.

The effect of drug therapy upon the group as a whole is shown in table 1. For the treated group, the cumulative survival rate was 68 per cent, while for the untreated group it was 48 per cent at the end of five years. Conversely, the respective death rates were 32 and 52 per cent. These differences are of high statistical significance.

Within each time period there were no significant differences in the rates between males and females (table 2).

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[1] Katz, J.: Am. Rev. Tuberc., 1952, *66*, 651.

TABLE 1

COMPARISON OF SURVIVAL RATES OF TUBERCULOUS MENTAL PATIENTS WITH AND WITHOUT DRUG THERAPY

Period After Diagnosis of Tuberculosis	Patients Receiving Drug Therapy (1950–1954)			Patients Not Receiving Drug Therapy (1941–1949)		
	Number of Patients Under Observation	Number of Deaths	Cumulative Survival Rate	Number of Patients Under Observation	Number of Deaths	Cumulative Survival Rate
years			*per cent*			*per cent*
0–1	981	184	81.1	1,851	607	67.2
1–2	662	43	75.8	1,143	138	59.1
2–3	443	11	73.9	952	77	54.3
3–4	323	15	70.4	683	37	51.4
4–5	169	5	68.3	445	25	48.5

TABLE 2

COMPARISON OF SURVIVAL RATES OF TUBERCULOUS MENTAL PATIENTS WITH AND WITHOUT DRUG THERAPY, BY STAGE OF DISEASE AT DIAGNOSIS, AND BY SEX

Period After Diagnosis	Cumulative Survival Rates (Per Cent)					
	With Drug Therapy			Without Drug Therapy		
	Total	Male	Female	Total	Male	Female
Minimal						
0–1	91.8	92.1	91.2	93.4	93.8	92.5
1–2	87.3	87.6	86.7	87.9	88.5	86.6
2–3	86.3	86.1	86.7	83.7	85.0	80.8
3–4	82.5	82.1	83.4	80.2	80.9	78.2
4–5	80.4	79.6	81.7	76.9	78.6	73.3
Moderately Advanced						
0–1	82.7	84.8	79.4	72.8	74.1	70.3
1–2	74.7	78.1	69.4	62.0	62.8	60.2
2–3	71.0	73.3	67.7	55.5	55.1	55.7
3–4	67.8	68.2	67.7	52.3	52.4	51.2
4–5	66.2	65.5	67.7	47.3	47.7	45.8
Far Advanced						
0–1	52.8	50.9	56.3	23.2	26.6	17.4
1–2	49.2	47.2	52.8	13.5	15.8	9.4
2–3	47.3	44.1	52.8	9.4	10.4	7.6
3–4	44.3	41.9	48.4	7.8	9.0	5.3
4–5	40.6	34.9	48.4	6.4	6.8	5.3

The beneficial effect of antimicrobial treatment is not evident among patients in the minimal stage of tuberculosis, but is statistically significant among those with more extensive lesions. Thus, 66 per cent of treated patients with moderately advanced pulmonary tuberculosis survived more than five years as compared with 47 per cent among

TABLE 3

NUMBER OF PATIENTS AT BEGINNING OF STUDY, 5-YEAR CUMULATIVE SURVIVAL RATES, 5-YEAR CUMULATIVE DEATH RATES, BY AGE AND STAGE OF DISEASE AT DIAGNOSIS — 1950–1954 AND 1941–1949

	Less than 25		25–44		45–64		65 and Older	
	1950–1954	1941–1949	1950–1954	1941–1949	1950–1954	1941–1949	1950–1954	1941–1949
Minimal								
Number of patients at beginning of study	23	37	166	397	213	315	94	100
5-year cumulative survival rate (per cent)	83.5	81.7	92.3	80.4	83.8	75.5	48.6	65.4
5-year cumulative death rate (per cent)	16.5	18.3	7.7	19.6	16.2	24.5	51.4	34.6
Moderately Advanced								
Number of patients at beginning of study	12	18	82	171	107	190	69	59
5-year cumulative survival rate (per cent)	100.0	21.4	84.2	49.6	68.7	51.6	33.8	37.8
5-year cumulative death rate (per cent)	—	78.6	15.8	50.4	31.3	48.4	66.2	62.2
Far Advanced								
Number of patients at beginning of study	15	27	74	256	61	230	52	78
5-year cumulative survival rate (per cent)	73.3	15.9	57.3	8.0	26.8	7.5	10.6	1.5
5-year cumulative death rate (per cent)	26.7	84.1	42.7	92.0	73.2	92.5	89.4	98.5

those not treated. The difference is much more pronounced among patients with far advanced disease, among whom the percentages were 40 and 6, respectively (table 2). Conversely, deaths were correspondingly higher in the untreated groups.

The number of patients in some age groups was too small to demonstrate statistically significant differences in survival rates, but, in general, the value of drug therapy was manifest at all ages less than 65 years (table 3).

Although not shown in tabular form in this report, both schizophrenic patients and those with other types of mental disease in the treated group had lower death rates than those with similar mental diseases who were not treated.

* * *

When the antituberculous drugs came into general use, there was some question of the duration of their beneficial effects. During the period of this study the duration of drug treatment kept up with the changing concepts of the need for their prolonged use. Thus, the short courses used at first gradually gave way to prolonged periods of treatment, up to a year or more. Had the effect of the drugs been temporary and limited to the period of treatment, deaths from tuberculosis would have been postponed for this period only.

That the beneficial effect extends considerably beyond the period of treatment is shown by the increased survival rates not only for the first year, but for all years up to the five-year maximal period of this study (table 1).

The therapeutic value of the drugs is more definitely shown among patients with advanced than among those with minimal disease.

In summary: The survival from tuberculosis of a group of mental patients, most of whom were treated with antituberculous drugs, was compared with that of a similar group not so treated. There was a significantly higher percentage of patients who survived five years among the treated patients. The effect of the drugs was most marked among patients whose disease was beyond the minimal stage.

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June 22, 1956

TOXICITY AND PHARMACOLOGY OF CYCLOSERINE[1]

Cycloserine is a new broad-spectrum antimicrobial drug with interesting properties.[2-13] Clinical studies indicate that cycloserine may be of value in the treatment of human tuberculosis and certain other infectious diseases.[13-21] It has been reported that under certain conditions the drug is capable of producing toxic effects in man.[22, 23] The present communication is concerned with the toxicity and pharmacology of cycloserine in animals.

The animals used in these studies were maintained in air-conditioned quarters and fed adequate stock diets and water ad libitum. Cycloserine, as the zwitter ion, was administered parenterally as a freshly prepared sterile aqueous solution. For intrathecal administration, the drug was dissolved in physiologic saline. In the experiments in which oral administration was employed, cycloserine was given either as a dry powder in capsules or as an aqueous solution. It was recognized that cycloserine may be labile in aqueous solution and hence care was taken to use the solution immediately after preparation.

Toxicity: The acute oral toxicity was determined in white mice (IS 32 strain) weighing between 18 and 20 gm. each and male rats (Holtzman strain) weighing between 140 and 160 gm. each. Observations were made at frequent intervals for the first six hours and thereafter once daily over a ten-day period. The effects of repeated oral administration were studied in young, growing male rats and in young dogs. Cycloserine was given to rats daily by stomach tube over a three-month period and to dogs in capsules over a three- to six-month period. Details of the amount of drug given are presented in the section dealing with results.

Clinical laboratory tests: In addition to the daily observations of the physical condition

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[1] This study was carried out with Oxamycin, the registered trade name of Merck & Co., Inc., for its brand of cycloserine.

[2] Harris, D. A., *et al.*: Antibiot. & Chemother., 1955, *5*, 183.

[3] Cuckler, A. C., *et al.*: Antibiot. & Chemother., 1955, *5*, 191.

[4] Cummings, M. M., *et al.*: Antibiot. & Chemother., 1955, *5*, 398.

[5] Shull, G. M., and Sardinas, J. L.: Antibiot. & Chemother., 1955, *5*, 198.

[6] Kuehl, F. A., Jr., *et al.*: J. Am. Chem. Soc., 1955, *77*, 2344.

[7] Hidy, P. H., *et al.*: J. Am. Chem. Soc., 1955, *77*, 2345.

[8] Stammer, C. H., *et al.*: J. Am. Chem. Soc., 1955, *77*, 2346.

[9] Welch, H., *et al.*: Antibiot. Med., 1955, *1*, 72.

[10] Barclay, W. R., and Russe, H.: Am. Rev. Tuberc., 1955, *72*, 236.

[11] Steenken, W., Jr., and Wolinsky, E.: Am. Rev. Tuberc., 1956, *73*, 539.

[12] Anderson, R. C., *et al.*: Antibiot. & Chemother., 1956, *6*, 360.

[13] Epstein, I. C., *et al.*: Antibiot. Med., 1955, *1*, 80.

[14] Herrold, R. D., *et al.*: Antibiot. Med., 1955, *1*, 665.

[15] Leon, A. P., and de Lourdes, M.: Rev. d. Inst. salub. y enferm. trop., 1955, *15*, 57.

[16] Ravina, A., and Pestel, M.: Presse méd., 1955, *63*, 1637.

[17] Lillick, L., *et al.*: Antibiots. Annual, 1955–1956, Medical Encyclopedia, Inc., New York, 1956, p. 158.

[18] Marmell, M., and Prigot, A.: Antibiots. Annual, 1955–1956, Medical Encyclopedia, Inc., New York, 1956, p. 153.

[19] Weiss, C.: J. Albert Einstein M. Center, 1956, *4*, 66.

[20] Kirshner, J. J.: J. Albert Einstein M. Center, 1956, *4*, 61.

[21] Epstein, I. G., *et al.*: Dis. of Chest, 1956, *29*, 241.

[22] Robinson, H. J., *et al.*: Antibiot. Med., 1955, *1*, 351.

[23] Kendig, I. V., *et al.*: Am. Rev. Tuberc., 1956, *73*, 438.

and behavior of the animals, the following examinations were made at regular intervals throughout the study: body weight; food consumption; hematologic studies, including erythrocyte, total and differential leukocyte counts, hematocrit, hemoglobin, and erythrocyte sedimentation rate. Biochemical tests of the blood included urea nitrogen, total proteins, albumin, globulin, alpha-globulin ratio, inorganic phosphorus, alkaline phosphatase, cholesterol, cholesterol esters, fibrinogen, and blood sugar. Frequent urinalyses were also performed.

Pathology: All animals were autopsied and the tissues were fixed in 10 per cent formalin or Bouin solution. The tissues were stained with hematoxylin and eosin. Examinations were made of the adrenals, aorta, bone marrow, brain, diaphragm, gall bladder, heart, kidney, small and large intestines, liver, lymph nodes, lung, pancreas, pituitary, prostate, skin, spleen, stomach, striated muscle, testes, trachea, thyroid, parathyroid, and urinary bladder.

Pharmacology: The influence of cycloserine on the blood pressure and respiration was determined in acute experiments, using cats anesthetized with pentobarbital sodium. Electrocardiograms were recorded at intervals throughout the experiments. Studies were also performed to determine whether cycloserine had any influence on the action of sympathomimetic or parasympathomimetic drugs or the autonomic blocking agents such as atropine and curare. In these experiments cycloserine was given both by stomach tube and by vein.

The additional pharmacologic studies included tests for antipyretic action, the effect on isolated guinea pig ileum, local action for irritation, and local anesthetic properties following instillation into the rabbit eye sac.

Mice and rats: Mice and rats given single oral doses of 2.0 gm. of cycloserine per kg. became depressed within thirty minutes, and the righting reflexes were abolished one to two hours after drug administration (table 1). The animals remained in a semicomatose state for five to seven hours, during which time they responded to painful stimuli. Doses of 3 to 4 gm. per kg. caused coma of longer duration and animals failed to respond to painful stimuli. At these higher dosage levels some rats failed to recover and died in coma. Except for mild congestion of the lungs and gastrointestinal tract, there were no striking gross or microscopic tissue changes at autopsy in mice or rats which died from a single dose of the drug.

Rabbits: The findings in rabbits differed from those noted in mice and rats in one important aspect. In this species, convulsive seizures were produced in some rabbits following oral and intravenous administration. Seizures were produced more readily if two to three daily intravenous injections of 0.75 to 1.0 gm. per kg. were given rather than administra-

TABLE 1

ACUTE ORAL TOXICITY OF CYCLOSERINE FOR MICE AND RATS

Dose	Number of Animals per Group	Per Cent Mortality		Remarks
		Mice	Rats	
gm/kg				
0.25	15	0	0	Slight depression
0.50	15	0	0	Slight depression
1.00	15	0	0	Transient coma
1.50	15	0	0	Transient coma
2.00	15	0	0	Transient coma
4.00	15	0	6	Deep coma
5.00	15	0	8	Deep coma

TABLE 2

CHRONIC ORAL TOXICITY OF CYCLOSERINE IN RATS

Dose	Number of Animals per Group	Initial Weight	Mean Weight in Grams—Weeks							
			1	3	5	7	9	11	13	17
gm./kg.		*gm.*								
0.1	35	148	182	232	280	302	316	345	349	390
0.3	35	144	168	227	272	304	324	341	354	381
0.6	35	143	174	222	263	291	314	337	348	373
1.2	35	145	160	214	257	272	288	315	324	357
Control	35	141	169	228	267	302	324	344	360	400

tion of the same total amount of drug as a single injection. Within one and one-half hours after the second dose of 1.0 gm. per kg. of cycloserine by vein, rabbits became weak and depressed, and within three to four hours the righting reflex was abolished. At the six- to seven-hour observation interval, rhythmic movements of all four legs were noted and the head was frequently deviated to one side. Convulsive seizures usually began as a running motion, followed rapidly by spasms of the muscles of the back which together with retraction of the head gave rise to typical opisthotonos. These seizures occurred at irregular intervals two to four times during the day on which the second dose of cycloserine was administered. Animals which died following the convulsive seizures showed marked congestion of the lungs, with considerable frothy fluid in the trachea and bronchial tree.

Intracisternal administration: Administration of 10 mg. per rabbit of cycloserine by the intracisternal route was lethal for rabbits within one to two hours. Rabbits developed typical convulsive seizures which were followed by deep coma and death. Doses of 5 mg. by this route of administration did not give rise to convulsive seizures, but caused a transient period of incoordination, head-drop, and muscular weakness. Such animals usually appeared normal the following day.

Chronic toxicity studies: Repeated daily feeding of cycloserine over a seventeen-week period to young male rats showed that doses as large as 300 mg. per kg. were tolerated without causing significant outward signs of toxicity. Larger doses of 600 to 1,200 mg. per kg. produced a slight to moderate depression in the rate of weight gain, but no other signs of toxicity (table 2). The hematologic, biochemical, and pathologic findings in these animals examined at two-, four-, eight-, twelve-, and seventeen-week intervals over the period of treatment revealed no significant abnormalities.

The first group of 4 male dogs was given 50 mg. of cycloserine per kg. every four hours around the clock. This dose level was approximately 3.0 gm. of cycloserine per dog per day. Under these conditions there were no outward signs of toxicity over a seven-day period. At this time the dosage regimen was changed to 1.5 gm. per dog twice daily and treatment was continued for an additional week. Here again, there was no evidence of toxicity and the dose level of cycloserine was increased to 1.5 gm. four times per day. This level was continued over a six-month period and, except for a few transient bouts of vomiting and mild diarrhea, there was no evidence of toxicity.

In a second group of 3 male and 3 female dogs dosed with 200 mg. per kg. twice each day over a four-month period, there were also no signs of toxicity. Hematologic and biochemical studies and urinalyses at monthly intervals in all 10 animals revealed no significant abnormalities.

Cardiovascular and respiratory system: When given orally in a dose of 1 gm. per kg. or 80 mg. per kg. by vein, cycloserine had no effect on the blood pressure in cats anesthetized

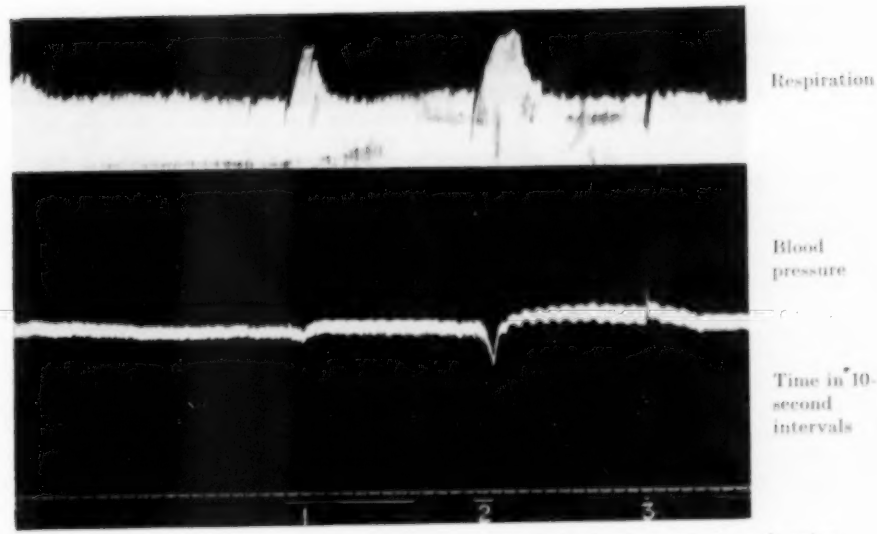

FIG. 1. Effect of cycloserine on blood pressure and respiration in a cat. 1—cycloserine, 200 mg. per kg. intravenously; 2—cycloserine, 400 mg. per kg. intravenously; 3—epinephrine-hydrochloric acid, 1 γ per kg.

with pentobarbital sodium. Intravenous injections of 200 to 600 mg. per kg., given in a volume of 5 to 10 ml. over a two-minute period, caused a rapid but transient fall in blood pressure ranging from 30 to 60 mm. of mercury (figure 1). During this period there were no significant changes in the electrocardiograms. Simultaneous observations on the respiration show that a dose as low as 40 mg. per kg. significantly stimulated the depth of respiration without altering the respiratory rate. Larger doses of cycloserine had a more profound effect and at the 400 mg. per kg. level the depth of respiration was essentially doubled. Here again the effect on respiration was transient, but was somewhat more prolonged than the blood pressure effect.

In the foregoing acute experiments cycloserine had no influence on the action of epinephrine and acetylcholine or on the autonomic blocking actions of atropine and curare.

Other pharmacologic tests: Concentrations of 0.5 and 1 per cent of cycloserine caused no local anesthetic action and no irritation when instilled into the eye sac of rabbits for a five-minute period. Similarly, doses of 200 mg. of cycloserine per kg. had no significant effect on the temperature response of rabbits when the cycloserine was given orally one hour before the intravenous injection of two standard units of pyrogen. Finally, concentrations of 0.5 mg. of cycloserine per ml. in Tyrode's solution caused a slight, but definite, reduction in the tonus of the isolated guinea pig ileum. In similar amounts, cycloserine appeared to moderately enhance the action of acetylcholine.

In summary: Cycloserine was well tolerated by mice, rats, rabbits, and dogs following single and repeated daily administration. Doses well above the therapeutic level caused no significant biochemical, histologic, or hematologic changes in rats or dogs after prolonged administration. Massive doses caused depression and coma in all of the foregoing animal species and induced convulsive seizures in some rabbits. The seizures noted in

rabbits were similar to those described in man and cats[24] and were produced by the oral, intravenous, and intracisternal routes of administration. Pharmacologically, cycloserine is essentially inert when given orally in therapeutic amounts to animals. Cycloserine may produce a fall in blood pressure and stimulate respiration when given in relatively small doses intravenously. However, these effects are transient, lasting for one to two minutes following the injection.

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HENRY SIEGEL

ALBERT EINSTEIN COLLEGE OF MEDICINE AND BRONX MUNICIPAL HOSPITAL CENTER
NEW YORK, NEW YORK

June 26, 1956

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[24] HAWKINS, J. E., JR.: Personal communication.

[25] The authors are indebted to Dr. Robert H. Silber for the biochemical determinations; and to H. F. Phares, J. J. Pietrowski, and F. T. Cuchie for valuable technical assistance.

THE COLLECTION OF SPUTUM FOR CULTURE OF MYCOBACTERIUM TUBERCULOSIS OBTAINED DURING LOCAL ANESTHESIA PRIOR TO BRONCHOGRAPHY AND BRONCHOSCOPY

The use of bronchoscopic aspiration of sputum, hypopharyngeal (laryngeal) swabs, and gastric aspiration for the detection of tubercle bacilli in patients who cannot raise sputum is well known. Another excellent source of sputum from patients who do not ordinarily cough can be collected just prior to bronchography and bronchoscopy. The instillation of a local anesthetic intratracheally produces violent coughing, and sufficient sputum can be obtained for bacteriologic examination.

For the past two years the writers have adopted the practice of collecting sputum routinely from those patients diagnosed as having nontuberculous pulmonary disease, or from known tuberculous patients whose sputum or gastric cultures have been negative for tubercle bacilli for more than six months. These sputum specimens were collected incidental to bronchography, which was clinically deemed necessary as a diagnostic or presurgical procedure. Of the one hundred and seventeen specimens submitted from bronchography, seven showed typical colonies of *M. tuberculosis*, ranging from one colony growth to 4-plus growth. Six of these patients never previously had cultures positive for tubercle bacilli, while one patient with pulmonary tuberculosis had negative gastric and sputum cultures for the preceding eleven months.

In summary: The collection of sputum during the anesthetic phase of bronchography or bronchoscopy is another excellent source of material for the bacteriologic diagnosis of pulmonary tuberculosis.

Pulmonary Disease and Laboratory Services
Veterans Administration Hospital
Albuquerque, New Mexico

Bernard Lowenstein
David Gale

July 30, 1956

Books

NOUVELLE ORIENTATION DU TRAITEMENT DU MAL DE POTT DE L'ADULTE. By S. DeSèze and J. Debeyre. Masson et Cie., Paris, 1956.

This short monograph presents the authors' experiences with the currently popular-in-Europe surgical management of tuberculous lesions of the spine. It is divided into two sections, the first of which deals with early diagnosis. DeSèze, who is the chief author of this part, is enthusiastic about the use of tomographs to show the skeletal lesion and believes in early open biopsy. Both authors emphasize the safety of opening tuberculous lesions, provided the patients have been previously treated with rest and drugs (PAS, streptomycin, and isoniazid in accepted dosages). For extensive lesions they recommend preoperative treatment for three to six months, but feel justified in going ahead after one month when the focus is a limited one.

The operative technique, which is different for each section of the spine, is described in detail by Debeyre in the second half of the monograph. He emphasizes the difficulties of approach and the limited visualization obtained. He believes that this method of treatment is preferable to the classic method of rest and fusion, since it evacuates abscesses, removes sequestra and necrotic debris, and allows the introduction of streptomycin by catheter irrigation into areas where it cannot diffuse from the blood stream. Bony cavities are filled with cancellous chip grafts, but the author does not think that intervertebral fusion is essential. It occurs only when the disc space is largely destroyed by disease.

Their results over the past three years are interpreted as favorable, though the authors themselves admit the inadequacy of the number and length of their follow-up observations. Comparison of results is made only with series of cases reported in the literature of patients who were treated by the standard fusion technique prior to the advent of streptomycin. Morbidity is claimed to be shorter but, when the types of lesions are considered, this does not seem to be very significant. The patients have had very little in the way of serious complications, and no dissemination of disease.

In concluding, the authors counsel against too rapid acceptance by the medical profession of what is in their minds an encouraging but unproved new surgical technique.

PHILIP D. WILSON, JR.
New York, New York

SPONTANHEILUNGEN DER LUNGENTUBERKULOSE. By Lasar Dunner, Head of the Industrial Chest Diseases Clinic, Hull, England. Pp. 59, with illustrations. Ferdinand Enke Verlag, 1955.

The author reports on long-term studies of 36 subjects during the course of spontaneous healing of their pulmonary tuberculosis. The clear presentation of the various stages of this clinical natural history is enhanced by the accompanying 75 chest roentgenograms.

OLE WASZ-HÖCKERT
Helsinki, Finland

BOOKS RECEIVED

OBSERVATIONS ON KREBIOZEN IN THE MANAGEMENT OF CANCER. By A. C. Ivy, John F. Pick, and W. F. P. Phillips. Pp. 88, Henry Regnery Co., Chicago, 1956. Price, $2.50.

INTERNAL SECRETIONS OF THE PANCREAS. Edited by G. E. W. Wolstenholme and Cecilia M. O'Connor. Pp. 292, Little, Brown and Co., Boston, 1956. Price, $7.00.

AGEING IN TRANSIENT TISSUES. Edited by G. E. W. Wolstenholme and Elaine C. P. Millar. Pp. 263, Little, Brown and Co., Boston, 1956. Price, $6.75.

CAUSAL FACTORS IN CANCER OF THE LUNG. By Carl V. Weller. Pp. 113, Charles C Thomas, Springfield, Illinois, 1955. Price, $3.00.

SUBPHRENIC ABSCESS. By H. R. S. Harley. Pp. 216, Charles C Thomas, Springfield, Illinois, 1956. Price, $7.00.

BIOCHEMICAL MECHANISMS IN INFLAMMATION. By Valy Menkin. Pp. 438, Charles C Thomas, Springfield, Illinois, 1955. Price, $9.50.

ARCHIVOS DE CLINICA MEDICA. By Juan Carlos Plá. Pp. 495, Centro de Investigaciones Clinicas, Montevideo, Uruguay, 1953–1954.

INTERNAL MEDICINE. By Robert P. McCombs. Pp. 706, Year Book Publishers Inc., Chicago, 1956. Price, $10.00.

AMBERSON LECTURE

The following are the opening remarks made on the occasion of the first Amberson Lecture, which was delivered by Dr. James Waring of Denver, Colorado. Dr. Waring's lecture is presented on pages 821 to 829 of this issue.

DR. RIGGINS: First, may I extend a warm welcome Dr. Amberson, Mrs. Amberson and their family;—also to the Bellevue family, members of the American Trudeau Society, National Tuberculosis Association, and guests. I should like just a minute to say something about how the Amberson Lecture came about. As the years rolled on, Dr. Amberson was the one at Bellevue who seemed to get younger, and the rest of us older, so time slipped up on us. Finally, however, we reminded ourselves that he was planning to retire. A committee was formed and, after careful thought and discussion, the committee in consultation with former and present members of the Visiting and House Staffs decided that the one thing Dr. Amberson would probably most appreciate, certainly the one thing that would best epitomize his dedication and devotion to medical education, would be the founding of an annual Amberson Lecture to be given by some noted medical educator, internist, or clinician at the annual meeting of the National Tuberculosis Association-American Trudeau Society. After considerable persuasion Dr. Amberson finally consented to the plan. And then with our friends in the National Tuberculosis Association-American Trudeau Society, arrangements were made so that the Amberson Lectureship is now a reality.

We are delighted to greet you at this first Amberson Lecture. However, before proceeding with the lecture, it is most appropriate and it gives me great pleasure to call upon the first Amberson chief resident and our good friend, Ted Badger of Boston, to say a few words for the Bellevue Group.

DR. BADGER: Thank you, Dr. Riggins. Dr. Amberson, Dr. Waring, Dr. McClement, and Dr. Perkins, ladies and gentlemen here in the audience. It is a very great pleasure and privilege today to talk to this audience for just a moment at this first lectureship to honor Dr. Amberson. As his first Bellevue resident, it is an honor to have this chance to express my gratitude to him for what I and many other young doctors in the past have carried away with us as patterns for the study and care of patients. As I look at Dr. Amberson today with his youthful appearance and his youthful mind, I sometimes wonder whether I am "his boy" or he is "my boy!" We started in together and sometimes it is a little hard to tell. I do think, however, that the establishment of this Amberson Lectureship is a most fitting expression of the inspiration that he has been to all of us as a teacher and as a physician. Dr. James Alexander Miller, who was desperate for a chief resident for his new service under Dr. Amberson, assigned me to it as the first resident although I knew absolutely nothing about tuberculosis or pulmonary disease. He suggested that I lessen my deficiencies by going to Trudeau Sanatorium for six weeks that summer, where I was exposed to the influence of Trudeau, Lawrason Brown, Fred Heise, and a host of other characters who are here in the audience today. By osmosis or diapadesis or some other means, I acquired some knowledge of thoracic diseases. But I can assure you that when I started on the Chest Service at Bellevue that autumn I still knew very little and there was a tremendous amount for Dr. Amberson to teach me. I should like also to extend my appreciation to Dr. Helen Pittman and Dr. Leroy Dunn, my juniors

in rank but my seniors in experience, for their tolerance and for all they taught me about tuberculosis and chest disease.

As one reviews one's educational past, the teachers who have been of influence in school, in college, and in medicine stand out in striking silhouette. Those things that Dr. Amberson has contributed to all of us as his students are not limited to chest disease and medicine alone, but include a portrayal of leadership into the realms of moderation and honesty in dealing with men and women. He has by precept shown us that the science and art of medicine are not found only in the physiological and the clinical laboratories or in the X-ray picture, but at the bedside of the patient and within the inquisitive minds of those physicians who spend their lives as students of medicine. It is this never-ending exploration into new fields of knowledge, in and out of medicine, that has been the greatest inspiration from the Bellevue adventure for this first resident of Dr. Amberson. There are two things about Dr. Amberson that remain very clear. The first is the fact that all of us know perfectly well that Dr. Amberson will never relinquish his thirst for teaching and retire, and the other is that remarkable and charming Mrs. Amberson. Thank you.

Dr. Riggins: Thank you, Ted Badger. You have spoken well for all Bellevue men and women, here and everywhere. It is now my privilege and pleasure to present to Dr. Amberson a brief citation, a few rather personal thoughts from the hearts and minds of members of previous and present House and Attending Staffs of the Bellevue Chest Service. Dr. Amberson, will you please stand.

TO JAMES BURNS AMBERSON
PHYSICIAN, TEACHER,
AUTHOR, FRIEND

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Of his Understanding of the Principles of Health,
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Of his Dedication to the Teaching of Scientific Medicine;
Of his Leadership without appearing to Lead;
Of his Human Interest and Understanding;
Of his Sincerity, Modesty and Dignity.

His Accomplishments and Way of Life have brought
Distinction and Honor to the Medical Profession.

Dr. Amberson: You will all forgive me if I do not make any attempt to express what I really feel. This is a fine and gracious thing which I appreciate much more than I can indicate by anything I can say. I would like to express my appreciation to the National Tuberculosis Association for offering to shelter this annual event which properly should be called "The Bellevue Chest Service Lectureship"; this to my mind would be much

more appropriate. Through the many years, all of us who have been working in the medical field in relation to the problem of tuberculosis and diseases of the chest have derived so much stimulus and inspiration from this Association, which I consider to be unique in the world. It has been a privilege to work with the Association and to acquire so many friends here. If this had been called the "Bellevue Lectureship" and I had been asked to give a lecture, I would have liked to talk about those who have come to the Chest Service and have gone out into this country and others to carry on the work in this part of the medical field. It has been a most unusual company of men and women and I consider it a rare privilege to have worked with them through these years. It has not been just a relationship of teacher and pupil; it has been much more than that. In other words, we worked together as partners. The men and women who came there stood out because of their interest, their eagerness, and their genuine humanity.

One question I always asked when a candidate came and applied for an appointment was why he wanted to come. In that way I acquired not only some knowledge of his motives, but also some understanding of his character which to me really determined his fitness. So we have now a group of Bellevue graduates and Bellevue candidates in training who represent in my judgment a rare company of men and women, true to the finest ideals of medicine. I can assure you with all honesty and candor they helped me much more than I ever helped them. They did it very gently. Thank you.

Dr. Riggins: Thank you, Dr. Amberson. As always, you have spoken feelingly, with characteristic humility and a youthful spirit. Now, on behalf of the Bellevue Chest Service graduates, founders of this lecture, it gives me both satisfaction and pleasure to present to Dr. James Perkins, our Managing Director, this check. Jim, on behalf of the Bellevue Chest Service I present you with a certified check made out to the National Tuberculos Association-American Trudeau Society for $8,033, the income from which is to be used in connection with the annual Amberson Lecture and for the continuing improvement of medical education and training in thoracic diseases.

Dr. Perkins: Dr. Amberson, Dr. Waring, Dr. Riggins, and other representatives of the colleagues and protegés of Dr. Amberson, and friends of Dr. Amberson. When Dr. Riggins first told me of this plan to honor Dr. Amberson upon his retirement from the Bellevue Chest Service, I was very much elated. Not only because I felt it a most worthy tribute to Dr. Amberson, but also because I felt it was equally a tribute to the National Tuberculosis Association and its medical section, the American Trudeau Society, to be designated as the medium for the expression of this warm love and respect. The National Tuberculosis Association and its medical section are greatly honored, I assure you, and we take very seriously the responsibility of handling this generous sum for the Bellevue group and of participating with and assisting them in choosing someone competent and worthy to be called the annual Amberson lecturer. We shall prove ourselves worthy of that trust, I assure you, and thank you very much indeed.

Dr. Riggins: Thank you, Dr. Perkins. When the time came for the Bellevue committee to select the first Amberson lecturer, by instinct I think all of us knew even before we gathered the one we would choose. However, being democratic, we searched the country and beyond the seas and unanimously concluded, as we knew we would, that the one and only man who should give the first Amberson Lecture was himself a great teacher and humanitarian, a long and respected friend of Bellevue, the American Trudeau Society, and of Dr. Amberson. After considerable persuasion and, he says, "with fear, trepidation and gratitude," he acquiesed. I am happy to present Dr. James Waring, the "dean of wit and wisdom," whom the Bellevue group has unanimously adopted as a fellow member.

Dr. Waring: Dr. Riggins, Dr. Amberson, and friends of Dr. Amberson. Before I

launch into my formal Amberson address, I would like to show you informally a few pictures of the "young" man. I might start off by saying that I have tried very hard to get, through sources that you might imagine, some intimate pictures of Dr. Amberson going all the way back to his earliest childhood. Unfortunately, the maternal instinct was strong in his family and I was not able to go back as far as I would have liked. But at any rate, I have some interesting pictures and Dr. Carr was good enough to stand by and help me show them. Dave, would you hold out please the last picture. The last slide is a kodachrome. Please hold that out. I shall refer to it later. The first picture, please. I think this is a very delightful picture of a young man, in his early days. I think you might call him at this time the budding student. Next slide, please; here he is a few years later and I think we might call him here the young doctor. The next slide; and here is a picture that is dear to my heart because he is fishing and I had him up with me in Colorado, but this was not in Colorado waters unfortunately; and I want him to come back sometime to show him how really to catch a trout. Next slide please; and here is a Spanish version of our "hero." I think it reminds me a little bit of Pancho Villa. However, I am not too sure. Next slide; and there is a wonderful picture of the Bellevue doctor and this to me, I think, shows wonderfully the expression of face, the thoughtfulness and kindness of his expression. I think this is the last one Dave. (May we have the lights please.)

I chose for the subject of my talk—a title of some sort had to be given, you cannot just call it the Amberson Lecture, and go on from there; you have to talk about something, you see. I have called it "The Chest Service at Bellevue Hospital—A Better Mousetrap."

At this point, Dr. Waring gave the first Amberson Lecture, presented in this issue on pages 821 to 829.

NOTICES

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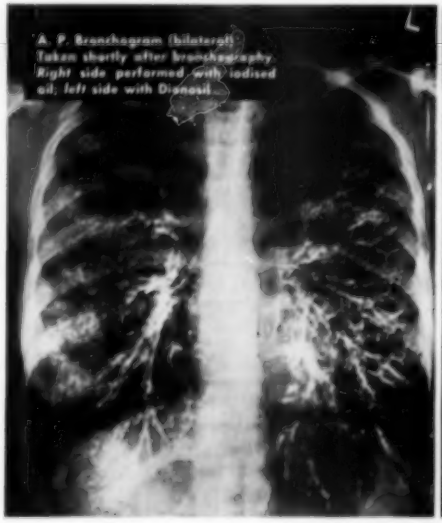
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